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The Journal of Pediatrics

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Original Communications

SULFONAMIDE DOSAGE IN EARLY INFANCY

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INTRODUCTION

RECENT investigations have presented definite evidence of the immaturity of renal function in the premature and the newborn infant.[1] It would seem, therefore, that the fate of drugs which depend predominantly upon renal excretion for elimination might be different in young infants than in older infants and children. Since sulfonamides are some of the more commonly employed drugs in this category, we were interested in re-evaluating dosage schedules of these compounds in the light of the newer information concerning renal function in early life. Our observations are the subject of this report.

MATERIALS AND METHODS

Our subjects consisted of fifty-seven infants ranging in age from 4 days to 8 months from the pediatric service of the University of Illinois Hospitals. The infants were free of acute infections, cardiac or renal abnormalities, metabolic disturbances, and dehydration. Only mature infants were included in this series. All other medications were withheld prior to and during our procedures.

Since West and his collaborators[2] have demonstrated that glomerular filtration may reach a mature level as early as 10 weeks of age, we were interested in observing any differences between infants below and above this age period. We arbitrarily decided to divide our subjects into those above and those below 2 months of age to see if differences might be reflected. Thus a group of infants ranging from 4 days to 2 months of age received single oral doses of sulfadiazine every twenty-four hours for several days. Each day 6- and 24-hour blood sulfadiazine levels were determined. A second group of infants ranging in age from 2 to 8 months was given similar doses of sulfadiazine. In a second group of experiments, infants were given single subcutaneous doses of a 5 per cent mixture of sulfonamides consisting of 2.5 per cent sodium sulfadiazine and 2.5 per cent sodium sulfamerazine in distilled water every twenty-four hours for several days. This mixture was utilized in an attempt to minimize the incidence of crystalluria and hematuria as suggested by Lehr.[3] The 6- and 24-hour blood levels were also determined in infants below and above 2 months of age.

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In all cases daily samples of urine were collected and checked for crystalluria and hematuria. The sulfonamide levels were determined on capillary blood by the method of Bratton and Marshall[4] using an Evelyn colorimeter. Duplicate blood samples were determined in all cases. The 24-hour blood levels were always obtained just prior to administration of the daily dose of sulfonamide. When sulfonamide mixtures were administered, blood levels were read in terms of sulfadiazine.

RESULTS

Group 1A.—Seven infants ranging in age from 5 days to 2 months were given a single dose of sulfadiazine orally starting with 0.13 Gm. per pound of body weight for the first 24-hour period and followed by 0.1 Gm. per pound of body weight, as a single dose, for each subsequent 24-hour period. The average blood sulfadiazine level at the end of each 24-hour period was 6.0 mg. per 100 c.c. with a range from 3.1 to 9.5 mg. per 100 c.c. The average sulfadiazine level at the end of the first 24-hour period was 5.9 mg. per 100 c.c., with a range from 3.1 to 9.5 mg. per 100 c.c. (Fig. 1, *A.*)

Group 1B.—Six infants in the group between 2 and 8 months of age on the same dosage schedule as the preceding group had an average sulfadiazine blood level at the end of each 24-hour period of 4.7 mg. per 100 c.c., with a range from 2.7 to 7.4 mg. per 100 c.c. The average 24-hour blood sulfadiazine level after the first 24 hours was 5.2 mg. per 100 c.c. with a range from 2.7 to 8.0 mg. per 100 c.c. (Fig. 1, *B.*)

Group 2A.—Six infants under 2 months of age were given 0.1 Gm. of sulfadiazine per pound of body weight orally as a single initial dose, followed by 0.064 Gm. per pound of body weight as a single dose for each subsequent 24-hour period. The average blood sulfadiazine level at the end of each 24-hour period was 4.8 mg. per 100 c.c. with a range from 2.5 to 8.8 mg. per 100 c.c. The average blood sulfadiazine level at the end of the first 24 hours was 4.4 mg. per 100 c.c. with a range from 4.0 to 6.4 mg. per 100 c.c. (Fig. 2, *A.*)

Group 2B.—Seven infants over 2 months of age were given the same dosage administered to Group 2, *A.* The average blood sulfadiazine level for each 24-hour period was 4.0 mg. per 100 c.c. with a range from 1.4 to 8.6 mg. per 100 c.c. The average of the blood sulfadiazine levels at the end of the first 24-hour period was 3.8 mg. per 100 c.c. with a range from 1.4 to 8.6 mg. per 100 c.c. (Fig. 2, *B.*)

Group 3A.—Ten infants under 2 months of age had an average blood sulfonamide level at the end of each 24-hour period of 8.3 mg. per 100 c.c. after receiving single injections of the subcutaneous sulfonamide mixture in doses of 0.032 Gm. per pound of body weight every 24 hours. The individual determinations ranged from 2.8 to 15.3 mg. per 100 c.c. The average blood sulfonamide level at the end of the first 24-hour period was 6.4 mg. per 100 c.c. with a range from 4.0 to 12.8 mg. per 100 c.c. The average blood level 6 hours after each dose of the sulfonamide mixture was 12.3 mg. per 100 c.c. with a range from 7.8 to 21.3 mg. per 100 c.c. (Fig. 3, *A.*)

Group 3B.—The average 24-hour blood level for the five infants over 2 months of age receiving the same dosage schedule as did Group 3*A* was 3.6 mg.

per 100 c.c. with a range of 2.8 to 4.5 mg. per 100 c.c. of sulfonamide. The average blood level at the end of the first 24 hours was 3.4 mg. per 100 c.c. with a range from 2.8 to 4.0 mg. per 100 c.c. The blood level 6 hours following each dose ranged from 7.6 to 11.7 mg. per 100 c.c. and averaged 10.0 mg. per 100 c.c. (Fig. 3, *B.*)

Group 4A.—Seven infants under 2 months of age in this group received a single daily subcutaneous injection of the 5 per cent sulfonamide mixture as a

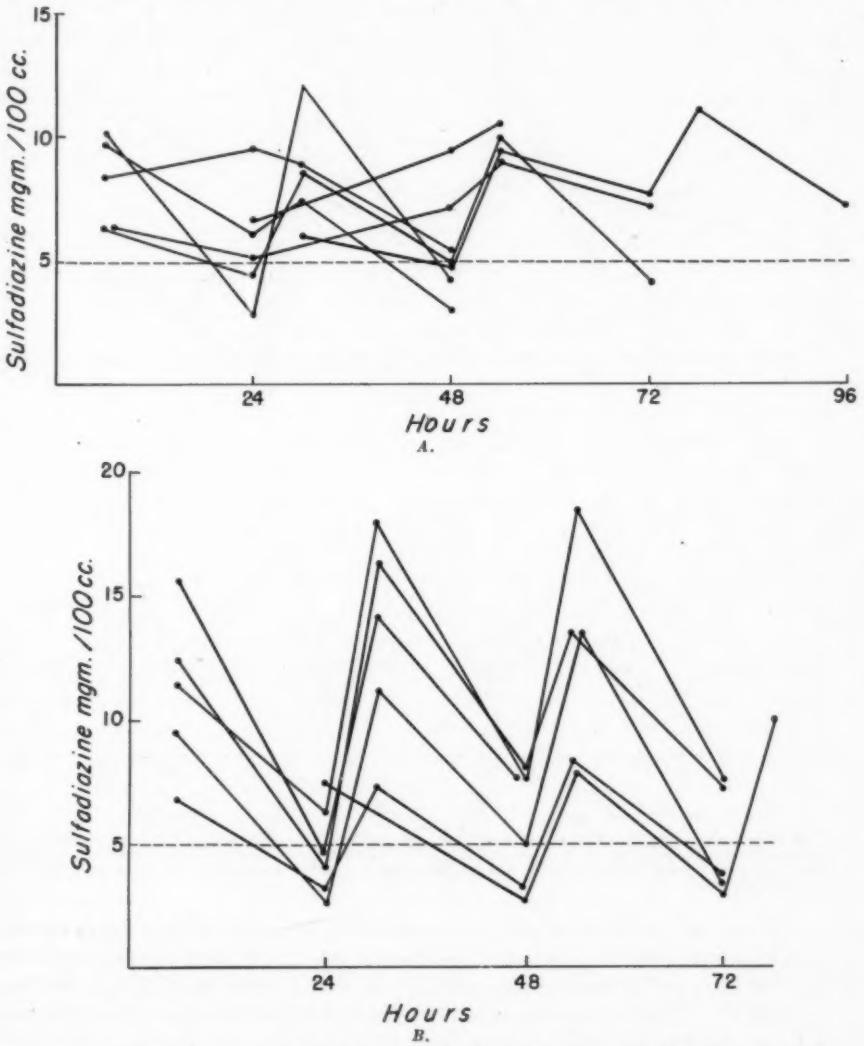
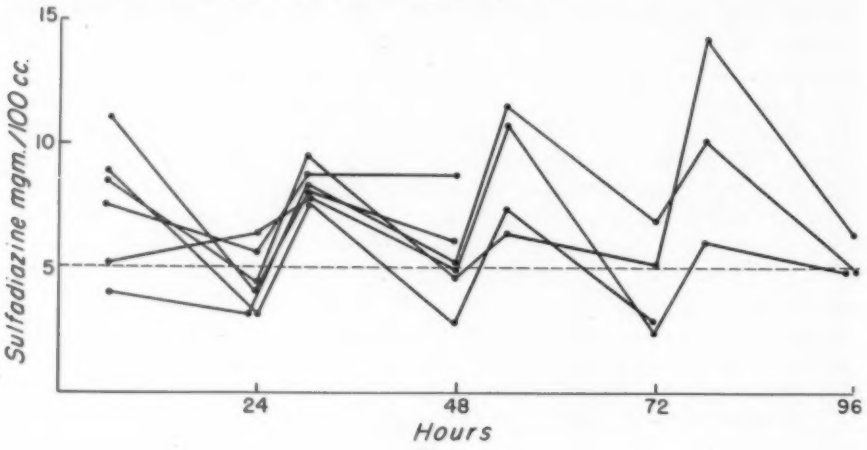


Fig. 1.—Dosage: 0.13 Gm. (2 grains) of sulfadiazine per pound of body weight administered orally for the first dose, followed by 0.1 Gm. (1.5 grains) per pound as a single dose every 24 hours thereafter. *A.* Seven infants under 2 months of age. *B.* Six infants over 2 months of age.

dose of 0.048 Gm. per pound of body weight. The average blood level at the end of each 24-hour period was 11.3 mg. per 100 c.c. with a range from 7.0 to 14.7 mg. per 100 c.c. The average blood level at the end of the first 24 hours was 10.3 mg. per 100 c.c. with a range from 7.0 to 15.1 mg. per 100 c.c. The blood level 6 hours after each dose ranged from 12.8 to 25.8 mg. per 100 c.c. and averaged 18.6 mg. per 100 c.c. (Fig. 4, *A*.)



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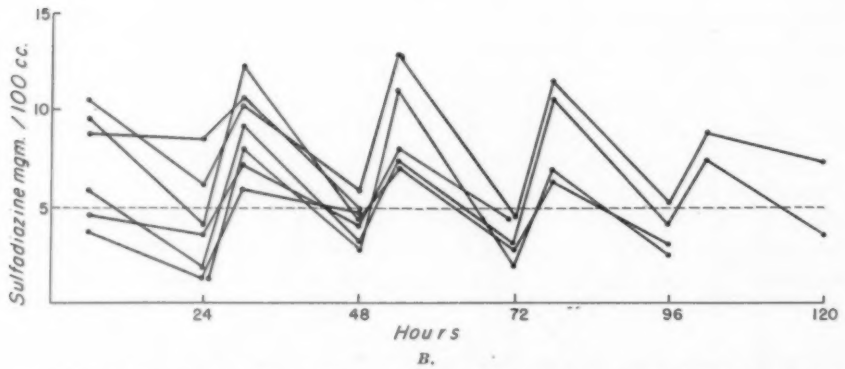

B.

Fig. 2.—Dosage: 0.1 Gm. (1.5 grains) of sulfadiazine per pound of body weight administered orally for the first dose, followed by 0.064 Gm. (1 grain) per pound as a single dose every 24 hours thereafter. *A*. Six infants under 2 months of age. *B*. Seven infants over 2 months of age.

Group 4B.—The same dosage administered to group 4*A* was administered to a group of nine infants above 2 months of age. The average blood level for each 24-hour period was 5.8 mg. per 100 c.c. with a range from 1.3 to 10.2 mg. per 100 c.c. The average blood level at the end of the first 24-hour period was 5.4 mg. per 100 c.c. with a range from 1.7 to 9.0 mg. per 100 c.c. The blood level 6 hours after each dose ranged from 10 to 22.8 mg. per 100 c.c. and averaged 15.8 mg. per 100 c.c. (Fig. 4, *B*.)

Examination of the urine was negative in all except two cases in which moderate crystalluria occurred. No gross or microscopic hematuria was noted. No local reactions were noted at the sites of subcutaneous injections.

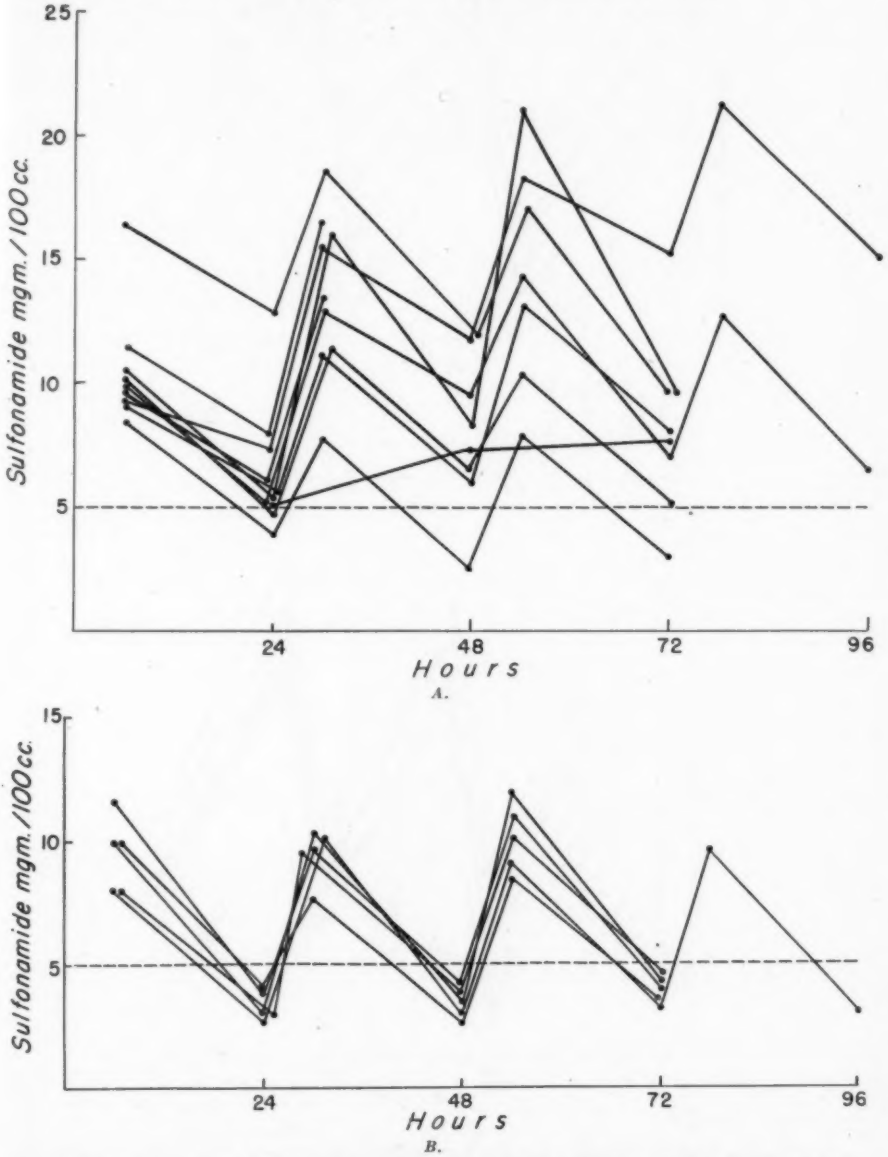

Fig. 3.—Dosage: Mixture of 5 per cent sodium sulfamerazine and sodium sulfadiazine, 0.032 Gm. (0.5 grain) per pound of body weight administered subcutaneously, as a single dose every 24 hours. *A*. Ten infants under 2 months of age. *B*. Five infants over 2 months of age.

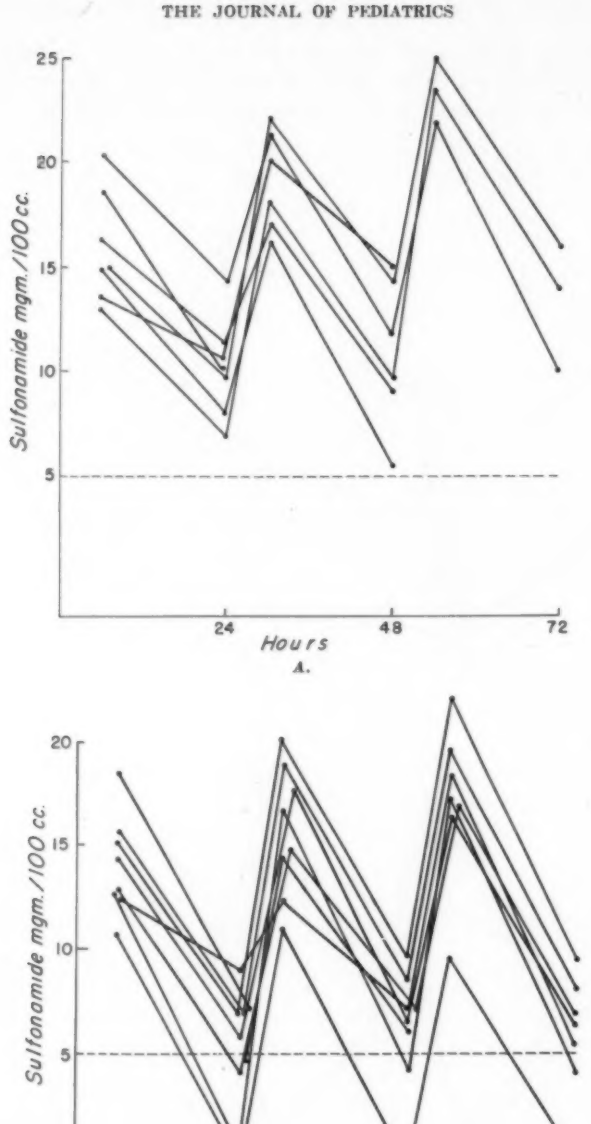

Fig. 4.—Dosage. Mixture of 5 per cent sodium sulfamerazine and sodium sulfadiazine, 0.048 Gm. (0.75 grain) per pound of body weight administered subcutaneously, as a single dose every 24 hours. *A*. Seven infants under 2 months of age. *B*. Nine infants over 2 months of age.

TABLE I

GROUP	NUMBER OF INFANTS	AGE OF INFANTS	DOSAGE (GM./LB. ONCE EVERY 24 HOURS)	ROUTE OF ADMINISTRATION	AVERAGE SULFONAMIDE LEVEL FIRST TWENTY-FOUR HOURS AND RANGE (MG./100 C.C. BLOOD)	AVERAGE SULFONAMIDE LEVEL FOR EACH TWENTY-FOUR-HOUR PERIOD AND RANGE (MG./100 C.C. BLOOD)	AVERAGE SULFONAMIDE LEVEL SIX HOURS AFTER EACH DOSE AND RANGE (MG./100 C.C. BLOOD)
1A	7	Less than 2 months	0.13 initially 0.1 daily thereafter	Oral	5.9 (3.1-9.5)	6.0 (3.1-9.5)	9.1 (6.4-12.0)
1B	6	Over 2 months	0.13 initially 0.1 daily thereafter	Oral	4.7 (2.7-7.4)	5.2 (2.7-8.0)	12.0 (6.7-18.3)
2A	6	Less than 2 months	0.1 initially 0.064 daily thereafter	Oral	4.4 (4.0-6.4)	4.8 (2.5-8.8)	8.5 (4.0-14.3)
2B	6	Over 2 months	0.1 initially 0.064 daily thereafter	Oral	3.8 (1.4-8.6)	4.0 (1.4-8.6)	8.3 (3.7-12.8)
3A	10	Less than 2 months	0.032	Subcutaneous	6.4 (4.0-12.8	8.3 (2.7-15.3)	12.3 (7.8-21.3)
3B	5	Over 2 months	0.032	Subcutaneous	3.6 (2.8-4.5)	3.4 (2.8-4.0)	10.0 (7.6-11.7)
4A	7	Less than 2 months	0.048	Subcutaneous	10.3 (7.0-15.1)	11.3 (7.0-14.7)	18.6 (12.8-23.8)
4B	9	Over 2 months	0.048	Subcutaneous	5.4 (1.7-9.0)	5.8 (1.3-10.2)	15.8 (10-22.8)

DISCUSSION

From our data it may be observed that, with one exception, infants under 2 months of age maintained satisfactory therapeutic blood sulfonamide levels with single 24-hour doses of 0.032 Gm. per pound of body weight administered subcutaneously. A satisfactory therapeutic blood level is generally considered to be a minimum of 5 mg. per 100 c.c. That age is a factor in the maintenance of the level is observed by contrasting the younger group with the group of infants over 2 months of age, none of whom had levels as high as 5 mg. per 100 c.c. 24 hours following administration of the same dosage schedule.

With a dosage of 0.048 Gm. per pound of body weight subcutaneously every twenty-four hours, the infants under 2 months of age maintained levels somewhat higher than the group on the lower subcutaneous dosage. This increased dosage also permitted the infants over 2 months of age to maintain satisfactory levels in 70 per cent of the determinations, although these levels were generally lower than those observed in the younger infants.

The infants receiving oral doses of sulfonamides generally had lower blood levels than those receiving subcutaneous medication in spite of considerably higher dosage. Although in many instances the blood levels were satisfactory at the end of 24 hours, this was not as consistently observed as with subcutaneous administration. This, combined with the relatively higher dosage necessary in oral administration, would tend to favor the subcutaneous route. Although we added sulfamerazine (which tends to promote prolongation of the blood level) to the subcutaneous mixture, the dosage did not seem adequate to account for the differences in results. These differences in results between oral and subcutaneous administration are not unexpected since Forbes and collaborators[5] have demonstrated that fecal loss of the drug tends to be greater in infants than in older individuals.

A review of the literature revealed little information regarding the administration of single daily doses of sulfonamides to infants followed by determinations of blood levels for a 24-hour period. Forbes and co-workers studied the effects of oral sulfadiazine in single doses in infants, but unfortunately did not observe results beyond 8 hours. Clarke[6] reported results of oral sulfadiazine administration in children, but presented no blood levels beyond 12 hours and no age group comparable to ours.

The higher levels of blood sulfonamide in those infants under 2 months of age given the sulfonamide mixture subcutaneously when compared to the blood levels of those over 2 months of age cannot be attributed to differences in subcutaneous absorption. Forbes[7] compared the absorption of subcutaneous sulfadiazine in infants, children, and adults and demonstrated that the most rapid absorption occurred in infants. The slowest absorption occurred in adults. One would expect, therefore, that with more rapid absorption the blood level would not be maintained as well in infants as in the older age groups. In this study the blood level in the newborn and young infant under 2 months of age was higher and was maintained longer than in the group over 2 months of age.

Slobody, Lehr, and Willner,[8] in their study of the administration of sulfonamide mixtures, compared young infants with older infants and children using

single doses of mixtures of sodium sulfamerazine and sodium sulfadiazine and observed the blood levels for 24 hours. They noted that the younger infants seemed to maintain blood levels as well or better than older infants even when the doses of sulfonamides given to the younger age group were smaller. Their detailed observations were made on six subjects, the youngest of which was 2 months of age, hence they presented no data on an age group comparable to our younger infants. They suggested that these results in infants might be due to renal immaturity.

Several groups of investigators within the past decade have established that the kidney of the newborn and young infant is functionally immature. McCance and his co-workers[9, 10] showed that the urea, sodium, and chloride clearances were all lower than the adult values even when the values were corrected for surface areas. Gordon and his group[11] corroborated McCance's findings of decreased urea clearances in the newborn period and also found that the urea clearances in the premature infant were lower than those of the newborn infant. In more detailed studies of glomerular and tubular function, Dean and McCance,[12] and West,[2] Barnett,[13] and Rubin[14] and their respective groups, have further demonstrated that renal function of the newborn and premature infant is lower than that of the adult. West and collaborators determined that at 10 to 20 weeks glomerular filtration approximates that of the adult and that at 30 weeks maximal tubular excretory capacity and renal blood flow attain adult values.

That renal function exerts an important effect in the maintenance of the blood sulfonamide level has been appreciated for some time. Long and Bliss[15] reported that an anuric patient given a single dose of sulfanilamide maintained a high blood level with slight variation for one week. Alyea and collaborators[16] showed that retention of sulfanilamide increased as renal function, measured by the phenolsulfonephthalein test, decreased. Kato[17] reported that the excretion of sodium sulfathiazole correlated with the urea clearance and could be used as a test of renal function.

Reinhold,[18, 19] Beyer,[20] and their groups, by employing clearance techniques, showed that sulfonamides undergo glomerular filtration and tubular reabsorption in much the same manner as urea. Since the urea clearance has been shown to be abnormally low in the premature, newborn, and young infant, we believe that our data indicate that sulfonamides also have a relatively low renal clearance during this period. This, we believe, explains the tendency for the maintenance of good sulfonamide blood levels on relatively low and infrequent doses which we have observed in the newborn and young infant.

Slobody, Lehr, and Willner[8] have already commented upon the practicality of administering intermittent subcutaneous injections of sulfonamide mixtures at 12-hour intervals and obtained good results in treating clinical infections. Glaser[21] also demonstrated that this is a practical technique for treating clinical infections. Our experience has verified the simplicity of administration by this route both in hospital and home practice. When the 5 per cent sulfonamide mixture of 2.5 per cent sodium sulfadiazine and 2.5 per cent sodium sulfamerazine in dosages employed in our studies are administered, the volumes for injec-

tion are relatively small. We avoided the incorporation of sodium sulfathiazole in our subcutaneous mixtures because of the local irritation which resulted from its administration in this concentration in the study of Slobody and his coworkers.

The low incidence of crystalluria and the absence of hematuria in our studies may be due in part to the fact that our subjects were not dehydrated or acidotic. Lehr[5, 6] has also directed attention to the efficacy of sulfonamide mixtures in minimizing crystalluria and hematuria. It should be emphasized that adequate therapy of dehydration and acidosis should be undertaken prior to sulfonamide administration.

CONCLUSIONS

Blood sulfonamide levels appear to be maintained at a higher level for a longer period in infants ranging in age from the newborn to 2 months than blood levels obtained under comparable conditions in older infants. In general the results with subcutaneous administration are more favorable and are more readily reproducible than those obtained with higher doses of orally administered drugs. This difference is presumably due to fecal loss of the drug with oral administration.

The subcutaneous administration of 0.032 Gm. per pound body weight of a 5 per cent mixture of equal parts of sodium sulfadiazine and sodium sulfamerazine in distilled water once every twenty-four hours maintained adequate therapeutic blood levels in infants under 2 months of age. The elevation of the dosage to 0.048 Gm. per pound body weight similarly administered effected higher blood levels in a similar age group. In addition, the infants over 2 months of age maintained therapeutic levels for 24 hours on this increased dosage in many instances.

The oral administration of sulfadiazine as an initial dose of 0.13 Gm. per pound body weight followed by 0.1 Gm. per pound every twenty-four hours maintained therapeutic blood levels in most instances in infants under 2 months of age. Slightly lower dosage was less effective. Because of the relatively larger dosage and greater variability of results, this route of administration is not suggested as preferable to subcutaneous administration in lower dosage as indicated above.

The maintenance of blood levels following single doses of sulfonamides in young infants as observed in this study is attributed largely to the immaturity of renal function during this age period.

SUMMARY

1. Blood sulfonamide levels following the administration of oral and subcutaneous sulfonamides were studied in fifty-seven infants ranging in age from 4 days to 8 months.

2. The blood levels in the groups receiving subcutaneous sulfonamides were superior to those receiving oral medication, although considerably lower doses were given, presumably because of incomplete intestinal absorption of orally administered sulfonamides.

3. Higher sulfonamide blood levels were noted in infants under 2 months of age receiving single doses of sulfonamides orally and subcutaneously when contrasted to older infants receiving the same doses. These differences are attributed largely to the immaturity of renal function in the younger infants.

4. No evidence of gross or microscopic hematuria occurred. Transient crystalluria occurred in two instances.

5. The practical application of the use of single subcutaneous daily doses of the sulfonamide mixture in young infants is discussed.

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CYSTIC TUBERCULOSIS OF BONE COMPLICATED BY TUBERCULOUS MENINGITIS

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IN 1928, Jungling[3] reviewed fifty-five cases of a disease entity in adults which he called osteitis tuberculosa multiplex cystica. The disease which he described consisted of cystic areas occurring predominantly in the small tubular bones of the hands. These areas varied in form on the roentgenogram. The absence of tubercle bacilli in the lesions, negative tuberculin tests, and negative guinea pig inoculations are inconsistent with the belief that the etiology was tuberculosis. The lesions in these cases remained stationary or healed slowly. Eighteen years later, Law and Perham[4] presented a paper in which they reviewed ten cases of multiple cystic tuberculosis of bone occurring in children. Six of these ten patients had positive tuberculin tests. Three of them had positive guinea pig inoculations, and involvement of the long bones was a common occurrence. Tuberculosis was obviously the most likely etiology of the lesions. Later authors, Sweet and Abramson[13] and Monfort and Solomon[11] expressed the belief that Jungling's disease and multiple cystic tuberculosis of bone were separate entities. Monfort and Solomon believed that Jungling's cases represented sarcoidosis. Eighteen cases classified as cystic tuberculosis of bone have been reported since 1928. Unlike Jungling's cases in which the long bones were rarely affected, 83 per cent of these eighteen patients showed involvement of the long bones of the upper extremities and 38 per cent of the patients showed lesions of the long bones of the lower extremities. Two-thirds of the patients had positive tuberculin tests and evidence of intrathoracic lymph node or pulmonary involvement. (See Table I.)

Study of all of the reports up to the present date disclosed no cases of this disease complicated by tuberculous meningitis. The following two cases, because of this additional complication, are therefore presented to demonstrate the radiologic changes that may be expected in this disease and also to show the course of the disease following streptomycin and Promizole therapy.

CASE REPORTS

CASE 1.—R. H., an 11-month-old Negro girl, was admitted for the second time to the Baltimore City Hospitals on June 21, 1948, with the chief complaint of swelling in her right hand and left foot of three weeks' duration. The patient was a twin born at home and brought to this hospital when 5 hours old. Her birth weight was 3 pounds, 8 ounces. The other twin died soon after birth. There was no history of familial disease and the prenatal course was supposedly uneventful. A serologic test for syphilis during the mother's seventh month of pregnancy was reported as negative. The child progressed satisfactorily

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in the hospital and was discharged on Aug. 31, 1947, at the age of one month, weighing 5 pounds, 7 ounces. The Eagle test taken at the age of 3 weeks was negative. The child remained well after discharge except for an occasional upper-respiratory tract infection and a recurrent papulovesicular rash over the back, which the mother related to baby foods.

The present illness began on May 30, 1948, when the child fell from her crib. Following this, the mother noticed that the left foot and the right hand were swollen and tender. The child refused to stand and refused to grasp objects with her right hand. Because these symptoms continued, she was brought to the hospital where an x-ray of her right hand showed a large cystic and expansile lesion of the third metacarpal with periosteal reaction along the shaft (Fig. 1, *A*). An x-ray of her left foot at this time showed radiolucent areas in the calcaneus and the first metatarsal (Figs. 2, *A* and 3, *A*), and an x-ray of her chest showed a widened mediastinal shadow with a deviation of the trachea to the right and an infiltration into the right upper lobe (Fig. 4, *A*).

On admission, the chief physical findings were a subsiding maculopapular rash over the back, slight dullness over the right posterior chest with a few dry inspiratory râles, a soft apical systolic murmur, a tender swelling of the dorsum of the right hand, and slight swelling of the left heel and foot.

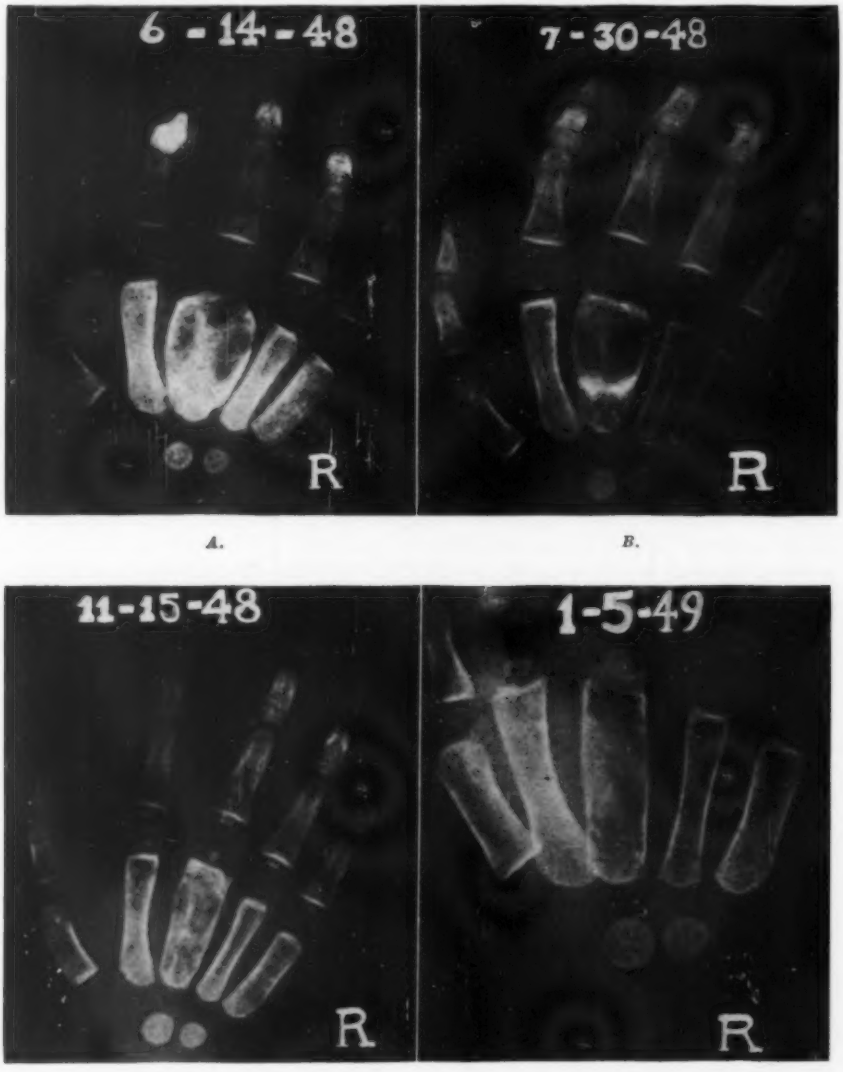
Laboratory Findings.—The laboratory findings were as follows: Urine, negative; red blood count 5.2 million; hemoglobin 6.8 Gm.; hematocrit 30 per cent; white blood count 11,350; differential 2 stabs, 53 segmented neutrophiles, 43 lymphocytes, and 2 monocytes. The blood smear revealed marked

TABLE I. BONES INVOLVED

AUTHORS	SMALL BONES OF HANDS	SMALL BONES OF FEET	LONG BONES UPPER EXTREMITIES	LONG BONES LOWER EXTREMITIES	T.B. IN CHEST	SKIN TEST	GUINEA PIG INOCULATION
Schwentker (1931)			+	+	+	+	+
Denks (1933)	+		+	+	+	+	
Acuni, Puglisi, and Vallino (1933)	+		+	+	-	+	+
Idem (1933)			+		-	+	
Bayer, W. (1933)	+	+			+	-	
Stallman (1934)	+					-	+
Petter, and Medelmann (1935)			+		+		
Vastine, and Bacon (1935)	+	+	+	+	+	-	
Idem (1935)	+				+	+	
Jacobsen (1936)	+	+	+	+	+	+	
Law, and Perham (1938)			+		+	+	
Thornton (1938)	+		+		-	+	
Martin (1939)			+		+	+	
Martin, and Fogel (1941)	+	+	+		+	+	
Sweet, and Abramson (1941)	+		+		-	+	+
Frost (1942)	+	+	+	+	+		
Monfort, and Solomon (1942)			+		+	+	
Birdsong, and L'Engle (1948)	+		+	+	-	-	

Table I summarizes the case reports of cystic bone tuberculosis in children reviewed by the authors. It illustrates: (1) the frequency of long bone involvement. (2) coincident intrathoracic tuberculosis, and (3) frequency of positive tuberculin tests.

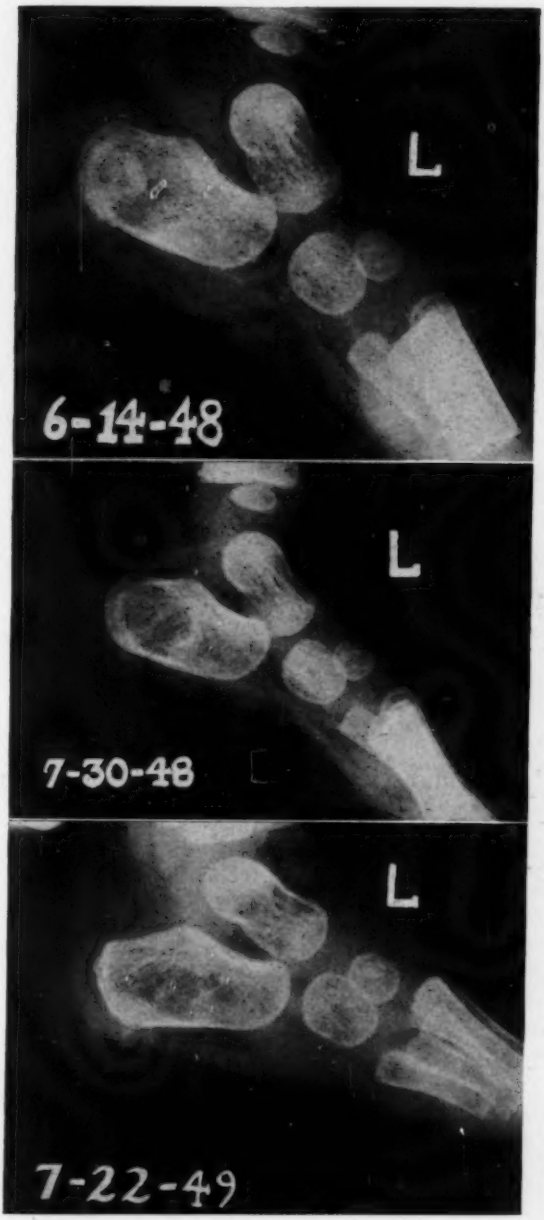
hypochromia and some anisocytosis. Sickle-cell preparations were negative. Serum analyses showed the following: sodium, 132 meq. per liter; potassium, 3.8 meq. per liter; chloride, 90.4 meq. per liter; carbon dioxide, 28.1 meq. per liter; calcium, 9.2 mg. per cent; phosphorus, 6.68 mg. per cent; alkaline phosphatase, 1.6 Bodansky units per 100 c.c.; cholesterol, 180 mg. per cent. Intra-



A. *B.*

C. *D.*

Fig. 1, *A*, *B*, *C*, and *D*.—Case 1. Films showing original cystic lesion in the third metacarpal undergoing progressive healing. The infection is limited by fibrosis and new bone formation resulting in a cystic lesion in the diaphysis instead of progressive destruction.

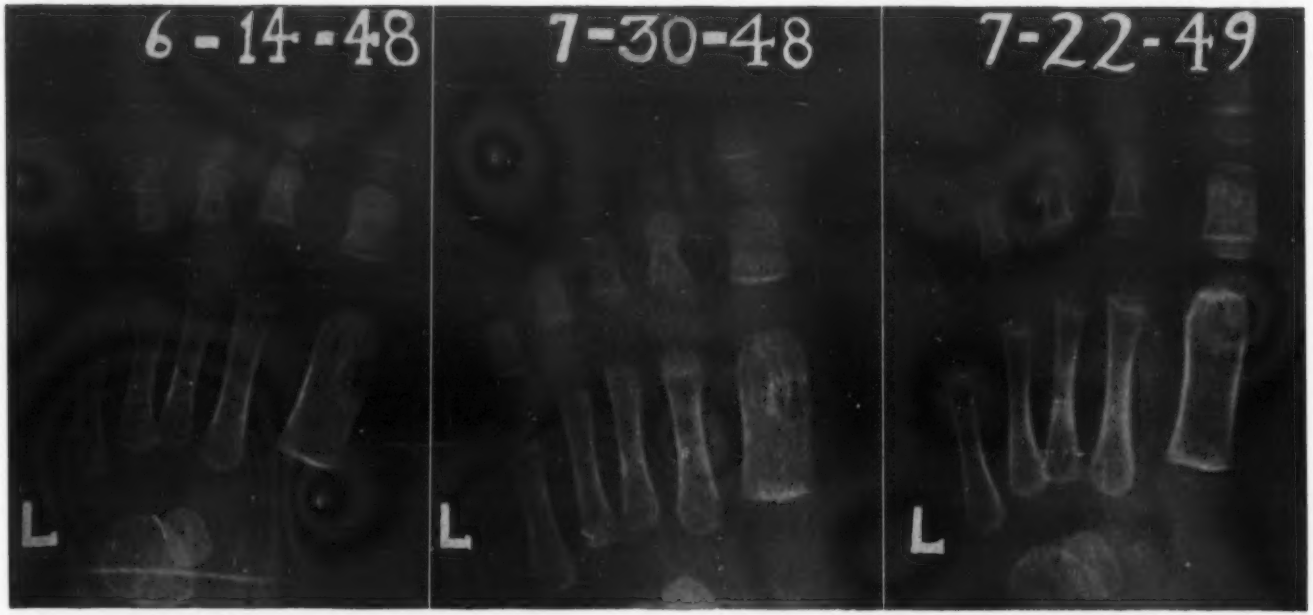


A.

B.

C.

Fig. 2, *A*, *B*, and *C*.—Case 1. Films of the left foot showing progressive healing of cystic lesions in the os calcis.



A. *B.* *C.*

Fig. 3, *A*, *B*, and *C*.—Case 1. Films of the left foot showing progressive healing of cystic lesions in the first metatarsal.

cutaneous reaction to 0.005 mg. PPD was strongly positive. A quantitative Eagle flocculation test revealed a titer of 256 plus, with a zone reaction. This was repeated with similar results. The findings in the cerebrospinal fluid on admission and on subsequent occasions are summarized in Table II. A complement-fixation test and a colloidal mastic test on the cerebrospinal fluid were negative. Smears, cultures, and animal inoculations of gastric washings and of cerebrospinal fluid were consistently negative.

TABLE II. CEREBROSPINAL FLUID EXAMINATIONS IN CASE 1 (R.H.)

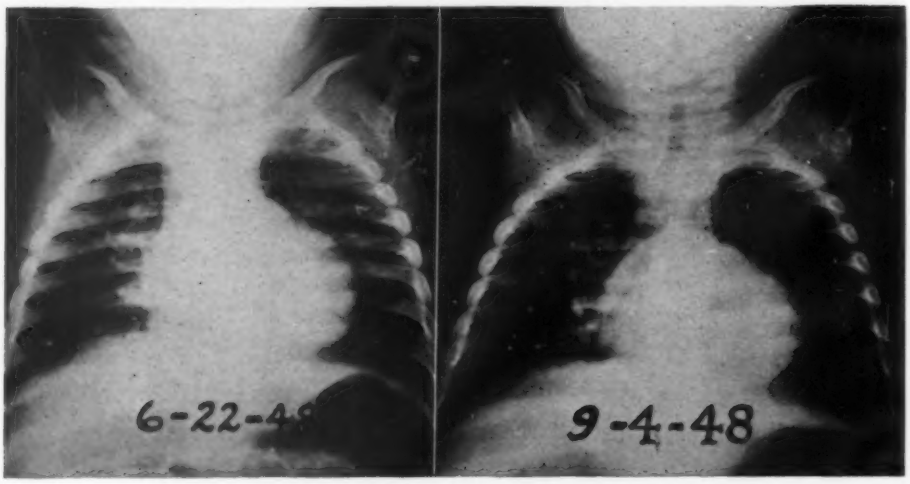
DATE	CELLS		PROTEIN (MG. %)	SUGAR (MG. %)	CHLORIDE (MEQ./L)
	NUMBER	% LYMPHOCYTES			
6-22-48	50	100	70	80	120.8
6-25-48	50	100	65	65	119.6
8-12-48	76	100	220	40	114.0
8-16-48	141	85	230	30	111.6
8-23-48	194	100	185	35	111.5
9- 9-48	40	100	160	35	120.8
9-25-48	40	100	120	75	118.4
10-22-48	12	100	70	55	127.6
1- 7-49	8	100	52	53	129.6
3-29-49	10	100	50	65	120.8
6- 9-49	0	0	48	62	121.6
7-11-49	0	0	50	50	119.6
8-25-49	0	0	35	65	127.6

Table II shows the cerebrospinal fluid findings before, during, and after intrathecal streptomycin therapy. On Aug. 12, 1948, when there was demonstrated a greater increase in the pleocytosis, a rise in the protein, and a fall in the sugar and chloride, intrathecal therapy was begun.

On the day after admission, the temperature rose to 106° F., and daily fever persisted for the next ten weeks. Because of the severe anemia, she was given two transfusions during the first week, and thereafter her hemoglobin remained above 11 Gm. When the mother's serologic test for syphilis was also found to be positive, the patient was given antisyphilitic treatment consisting of 100,000 units of penicillin per kilogram, divided into 120 doses at intervals of two hours. X-rays of the lower extremities on the sixth day after admission (Fig. 5, *A*) showed a cystic area in the metaphysis of the right tibia.

Streptomycin intramuscularly was started on June 30, 1948, in the dosage of 50 mg. per kilogram per day. Because of difficulty in obtaining the antibiotic at this time, it had to be discontinued after three weeks. Promizole was also started, and because of the extremely rapid renal clearance of this substance (in marked contrast to Case 2) 5,000 mg. per day were necessary to maintain adequate serum levels.

Although the cerebrospinal fluid on admission showed a moderate pleocytosis, the protein was not markedly elevated, the sugar was normal, and there were no meningeal signs. In the course of the next month, however, clinical signs of meningeal irritation gradually appeared. Three and one-half weeks after intramuscular streptomycin was discontinued, a marked elevation of the cerebrospinal fluid protein, and a fall in the sugar occurred which strongly suggested tuberculous meningitis. Although a pellicle formed, smears and cultures failed to demonstrate the tubercle bacillus. Streptomycin was then begun intrathecally, 25 mg. every day for two weeks, then every other day for seven weeks, following which the cerebrospinal fluid became more nearly normal. On Oct. 24, 1948, because of the extension of the tuberculous infection in the right lung field and the rapid destruction of the distal end of the left femur (Fig. 5, *B*), intramuscular streptomycin was again started and continued for three months. On Dec. 7, 1948, because of marked destruction of the distal end of the left



A. B.

C.

Fig. 4, *A*, *B*, and *C*.—Case 1. Films of the chest showing infiltration in right-upper lobe in the initial films. This cleared on streptomycin and supportive therapy.

femur, a plaster hip spica was applied. Three weeks later, an x-ray of the left leg showed a fracture of the tibia below the level of the hip spica (Fig. 5,*C*), apparently incurred when the patient was being turned in bed. A longer cast was therefore applied to include the fractured tibia and this was not removed for three months. By January, 1949, x-rays of the hands showed normal bone structures. In February, 1949, most of the other bony lesions were beginning to show healing, and the chest x-ray showed a resolution of the infiltration in the right middle lung field. She was discharged from the hospital on April 28, 1949, with continued administration of Promizole, 5,000 mg. per day, at home.

The patient has been seen regularly in the outpatient department, and follow-up x-rays show further healing of the bones (Figs. 1 through 5,*B*, *C*, and *D*). The cerebrospinal fluid continues to be normal in every respect. A titrated Eagle flocculation test shows a titer of 3.

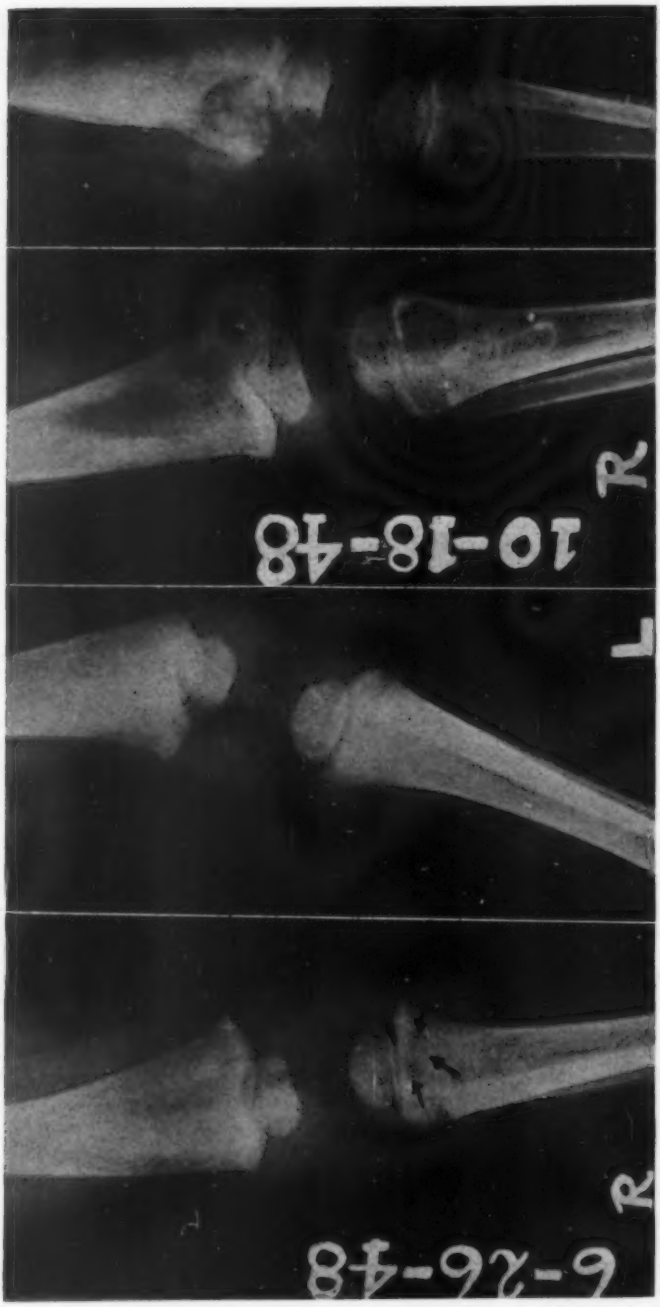
CASE 2.—B. C., a 21-month-old Negro female child, was admitted to the Baltimore City Hospitals on Sept. 8, 1948. Her present illness began five months previously, when two weeks following a fall, she guarded all movement of her right arm. At the time, the fall was considered trivial. She was taken to another hospital on April 19, 1948, where x-rays of the right wrist showed "periostitis" and an x-ray of the chest showed "hilar adenopathy and infiltration in the left lower lobe." A return appointment was not kept, and the child was not seen again until five weeks later on May 28, 1948, when x-rays of the right arm showed "rarefaction along the middle one-third of the radius." A tuberculin test using 0.01 mg. O.T. (old tuberculin) was negative at this time. She was seen six weeks later when on July 9, 1948, a tuberculin test with 0.1 mg. was positive. X-rays at this time revealed "multiple lesions of the right ulna, radius, and metacarpals." In the next two months she gradually became listless, apathetic, anorexic, and developed a constant hacking cough. Two days before admission she developed a high fever, became progressively dyspneic, and finally she was sent to the Baltimore City Hospitals for admission.

Her grandfather, with whom she had been in close contact, had died of active tuberculosis two weeks before the patient's admission to the hospital.

On admission, the child was fairly well nourished but appeared to be acutely ill. Her rectal temperature was 104.2° F., her pulse was 100, and her respirations were 42 per minute. The chief physical findings were confined to the chest and the right arm. There was diminished excursion of the left chest. The percussion note was flat, and there was greatly decreased tactile and vocal fremitus as well as diminished breath sounds over this entire side. The mediastinum was shifted to the left. The right arm was held out stiffly from the body, and movement of the wrist caused pain. The wrist and the entire hand were moderately swollen, and there were markedly enlarged epitrochlear and axillary nodes on the right.

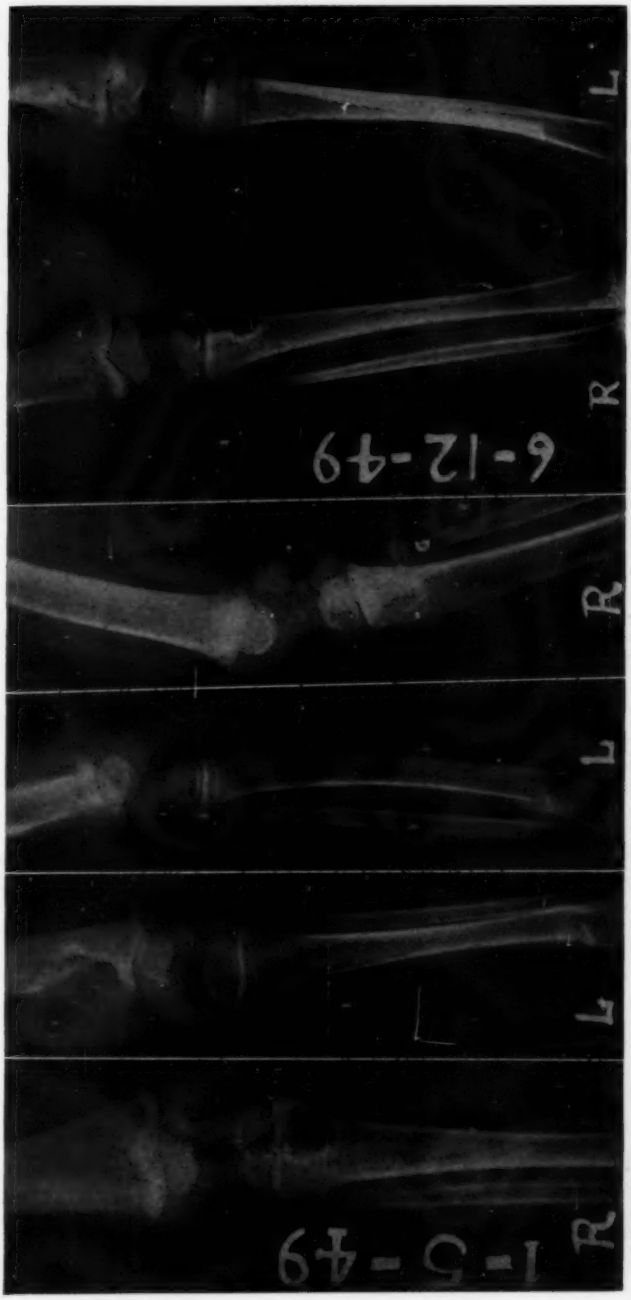
Laboratory Findings.—The laboratory findings were as follows: Urine negative except for a one-plus albumin; red blood count 4.9 million; hemoglobin 9.5 Gm.; hematocrit 32 per cent; white blood count 39,000; differential 3 myelocytes, 15 stabs, 65 segmented neutrophiles, and 17 lymphocytes. The erythrocytes appeared to be markedly hypochromic. Sickle-cell preparations were negative. The sedimentation rate was 35 mm. per hour (corrected), and the Wassermann and Eagle tests were negative. Serum analysis: sodium, 135 meq. per liter; potassium, 4.0 meq. per liter; chloride, 102.4 meq. per liter; carbon dioxide, 21.2 meq. per liter; calcium, 8.8 mg. per cent; phosphorus, 4.67 mg. per cent; and alkaline phosphatase, 4.83 Bodansky units per 100 c.c. Intracutaneous reaction to PPD 0.00002 mg. was positive. Tubercle bacilli were cultured from the gastric washings. The changes in the cerebrospinal fluid are summarized in Table III. An x-ray examination of the chest showed a homogeneous density throughout the entire left hemithorax with mediastinal shift to the left and infiltration throughout the right mid-lung field (Fig. 6,*A*). X-rays of the osseous lesions are shown in Figs. 7, *A*, 8, *A*, and 9.

Because of the possibility of some secondary infection in the lungs, penicillin, 20,000 units every three hours, was started. At the end of one week there was no improvement, and daily temperature spikes, as high as 104° F. on occasions, were recorded. On Sept. 16, 1948, streptomycin was begun in the dosage of 50 mg. per kilogram per day; within five days the temperature had fallen to normal and there was no elevation over 100° F. for the next four months.



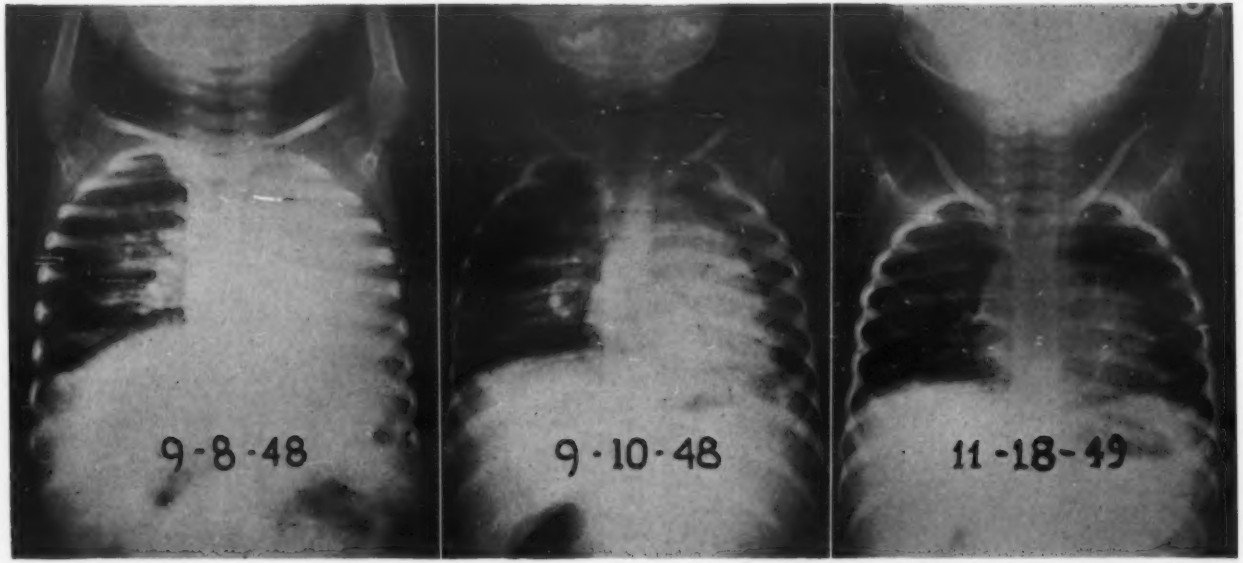
B.

A.



C. D.

Fig. 5, *A*, *B*, *C*, and *D*.—Case 1. Serial x-rays of the knees showing response to therapy. Note fracture of tibia (5, *C*) which was an incidental finding. This fracture occurred below the end of the cast and required replacement of the original cast by a longer one.



A. *B.* *C.*

Fig. 6.—Case 2. *A*. X-ray of the chest showing bilateral tuberculosis with atelectasis of the entire left lung. *B*, and *C*. X-rays showing re-expansion of the left lung and resolution of the infiltration in the right lung.

TABLE III. CEREBROSPINAL FLUID EXAMINATIONS IN CASE 2 (B.C.)

DATE	CELLS		PROTEIN (MG. %)	SUGAR (MG. %)	CHLORIDE (MEQ./L.)
	NUMBER	% LYMPHOCYTES			
9-15-48	40	90	55	80	127.6
10- 1-48	7	100	56	53	125.3
10-13-48	11	100	65	70	124.8
10-22-48	23	100	50	62	129.6
11-22-48	28	100	48	55	129.6
12-21-48	60	100	60	72	131.6
1-13-49*	240	98	120	35	122.4
1-17-49	250	92	130	30	123.6
1-23-49	420	88	146	25	123.6
1-28-49	600	70	150	30	120.8
2- 4-49	520	74	155	40	117.6
2-18-49	450	51	115	35	122.8
3- 6-49	700	42	118	38	118.8
3-16-49	385	74	112	60	123.6
4- 1-49	104	84	114	40	121.6
4-21-49	74	94	60	50	121.6
5- 5-49	28	86	50	70	122.8

*Tubercle bacilli isolated by culture and guinea pig inoculation on this date. Intrathecal streptomycin therapy started the next day.

Table III shows the cerebrospinal fluid findings before and after intrathecal streptomycin therapy. Noteworthy is the fact that three weeks following the completion of a ninety-day course of intramuscular streptomycin, meningitis developed.

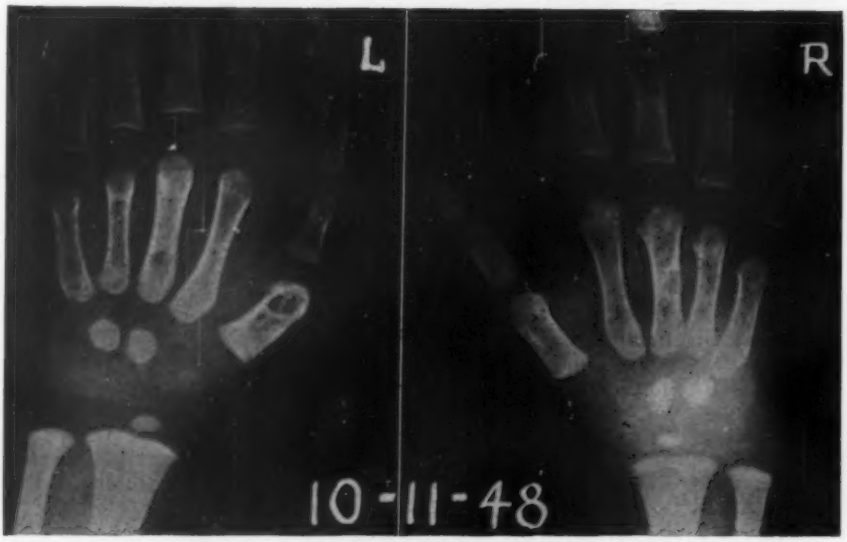
On Sept. 26, 1948, Promizole was begun, 500 mg. per day, and satisfactory levels were maintained in the blood (from 3 to 4 mg. per cent) and spinal fluid (from 1 to 2 mg. per cent).

The left lung gradually re-expanded during the next few months (Fig. 6, *B* and *C*). The tenderness of the right wrist disappeared rapidly, although the swelling persisted for some time. The x-ray changes are shown in Fig. 7, *B*, *C*, and *D*.

On Dec. 26, 1948, after a three-month course, streptomycin was discontinued. During the period of intramuscular streptomycin treatment, repeated lumbar punctures had continued to show some pleocytosis and a moderately elevated protein. Repeated smears, cultures, and guinea pig inoculations, however, failed to show any tubercle bacilli. It was felt that this perhaps represented a "serous meningitis" as described by Lincoln.[7] On Jan. 5, 1949, however, the temperature rose, signs of meningitis developed in a few days, which were confirmed by the cerebrospinal fluid findings. Culture of the spinal fluid was positive for tubercle bacilli. Streptomycin was again administered in the same dosage intramuscularly, along with 25 mg. of streptomycin intrathecally every day for three weeks, then every other day for six more weeks. After a long, stormy, and febrile course, the patient showed improvement and became asymptomatic. Intramuscular streptomycin was discontinued on April 16, 1949, but the Promizole was continued. The course throughout the remaining six weeks of hospitalization was uneventful, and the patient was discharged on May 23, 1949.

It was intended that the child be maintained on Promizole therapy after discharge for about two years. However, the mother failed to bring the child back to the outpatient clinic until Aug. 12, 1949, and she had not taken any Promizole for over a month. At this visit she was febrile and had signs and symptoms of meningitis with typical spinal fluid findings. She was readmitted to the hospital for treatment of her meningitis and, at the present time, she has completed a three-month course of treatment with streptomycin with apparent recovery. The pulmonary and osseous lesions appear to be quiescent (Figs. 6, *C*, 8, *B*, and 9, *B*).

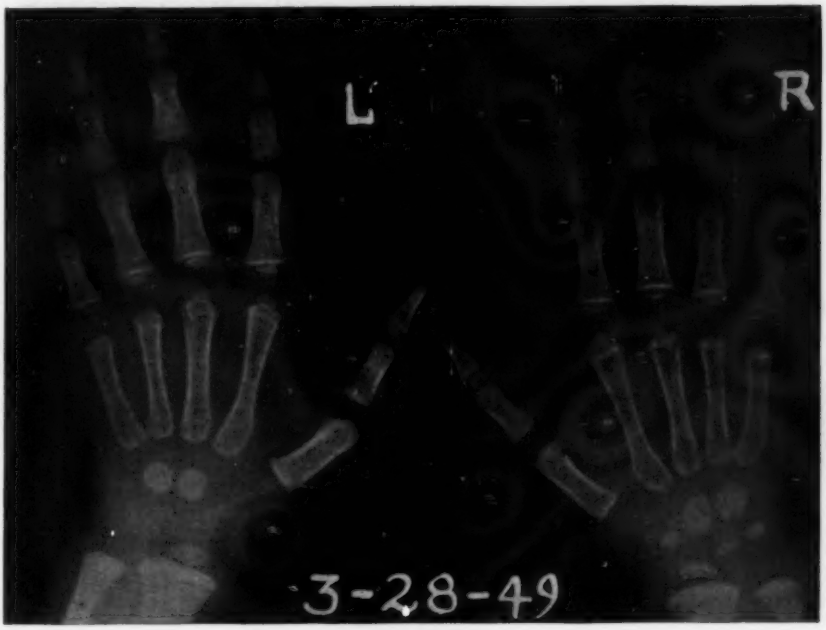
A.



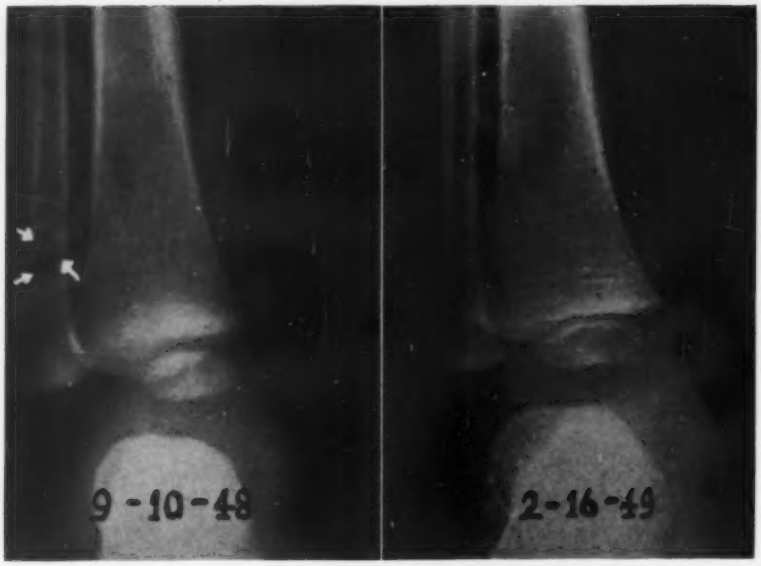
B.

Fig. 7. *A*, *B*, *C*, and *D*.—Case 2. Serial films of the hands showing original cystic lesions of the left first metacarpal and right carpals undergoing progressive healing. Note the earlier calcification of the right carpal bones as healing progressed when compared to the left.

C.



D.



A. *B.*

Fig. 8.—Case 2. *A.* X-rays showing original lesion of the right fibula. *B.* Same area healed.

A. *B.*

Fig. 9.—Case 2. *A.* Shows cystic lesion of the right first metatarsal and tarsal. *B.* Same areas healed.

COMMENT

In children, as in adults, tuberculosis of the bone is usually secondary to pulmonary tuberculosis. Tubercle bacilli metastasize from their source in the lung and intrathoracic lymph nodes to bone and, because of the position of the end arteries, they most frequently lodge in the metaphyseal region of the shaft.[4] Typical tubercles are formed and usually caseation necrosis and destruction of the bone occurs. There is often epiphysitis in addition to metaphysitis and the involvement may extend into the joint. When necrosis occurs more rapidly than fibrosis, there is destruction of the bone. Infrequently fibrosis occurs more rapidly than necrosis and circumscribed lesions result which appear as cystic areas on the x-ray examination.

Involvement of the diaphysis occurs in the same manner; however, the resulting lesion is modified by the presence of the periosteum which limits the lesion by the formation of new bone. In the diaphysis, as in the metaphysis, the inflammatory process may be so overwhelming that necrosis and even abscess formation may occur. If fibrosis and new bone formation are adequate, cystic lesions occur in the diaphysis instead of progressive destruction.[12] These lesions are usually fusiform in shape and are seen on roentgenograms as well-demarcated areas of decreased density in the shaft with thinning of the cortex and sometimes with expansion of the shaft.

Because of the hematogenous spread of the tubercle bacilli, multiple lesions frequently occur. It has been pointed out by Martin and Fogel[9] that all primary tuberculosis causes blood-stream infection and that usually, the lesions of the bones and viscera are overcome and healed. They state further that only when the resistance of the bone has been lowered by previous trauma or disease does multiple cystic tuberculosis occur. Frost[1] agrees with Martin and Fogel and reports a case of multiple cystic tuberculosis of bone associated with congenital syphilis. In the two cases reported above, one patient had congenital syphilis and the other presented a history of a fall.

SUMMARY

Two cases of multiple cystic bone tuberculosis complicated by tuberculous meningitis have been reported in detail. The course of the disease is demonstrated by serial x-rays taken at intervals over a period of thirteen months and seventeen months, respectively. Both patients were treated with streptomycin and Promizole with healing of the bone lesions and remission of the meningitis.

Since the completion of this article, Turkish, Murphy, Roody and Saigh[16] have reported one additional case of this disease.

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PSEUDOHYPOPARATHYROID TETANY

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IN 1942 Albright, Burnett, Smith, and Parson[1] described three patients, two adults and a child, in whom tetany was associated with hypocalcemia and hyperphosphatemia. The principal feature which distinguished the cases from true hypoparathyroidism was the failure to respond to parathyroid extract in the usual way, i.e., with an increased output of phosphorus in the urine and an elevation of the serum calcium. Two patients were operated upon and intact parathyroid glands were found without difficulty. One showed normal parathyroid tissue, the other showed hyperplasia.[2]

The patients presented other features not ordinarily seen in true hypoparathyroidism. They were short, thick-set, and had round faces; and there were abnormalities in the length and configuration of the hand bones, especially the metacarpals. Areas of calcification were visible in the soft tissues. The patients responded to dihydrotachysterol (AT-10) with an elevation of the serum calcium, but the response was less rapid than that ordinarily seen in true hypoparathyroidism. The authors inferred that the primary defect is not the failure to produce parathormone but, rather, an inability of the receptors to respond to it.

Since his original report, Albright[2] has seen a fourth case, and he mentions three others observed, respectively, by Dr. Edward E. Beard of Cleveland, Dr. Randall G. Sprague of the Mayo Clinic, and Dr. John S. L. Browne of Montreal. In Browne's patient the mother showed abnormalities of the metacarpal bones, but there was no opportunity to investigate the possibility of pseudohypoparathyroidism in her. The condition is of special interest to the pediatrician since the onset is usually in childhood.

CASE REPORT

M. C., a 16-year-old girl, was first seen at the age of 14 years because of convulsive seizures of three months' duration. The seizures were preceded by an aura which consisted of the desire to sleep. A tonic phase was followed by a clonic phase, after which the patient was exhausted and slept. Bodily injury or incontinence did not accompany the seizures. From time to time there were minor attacks during which the patient stood still for a moment, dropped a fork or a spoon, and so on. She also had attacks in which her left hand and foot would point inward and during which she would not respond to questions or directions. She once seemed confused, walked into a wall and tried to walk out of a fourth story window. She would sleep after attacks. The seizures took place about every six weeks. There was no tingling or paresthesia.

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Margaret was the second of four siblings. The oldest, a boy of 18 years, matured at an early age and had hair on his chest at 12 years. He was unusually large and, at the age of 9, worked in an ice house. A younger sister, aged 15 years, had her menarche at 7 years and regular menses since the age of 8 years. The youngest sibling, a girl aged 14, was normal except for slowness in school. The mother was 36 years of age and very short. She was normally proportioned and in good health except for chronic arthritis. The father was 39 years old, unemployed, and alcoholic.

Margaret's prenatal and birth histories were normal. Her weight at birth was 7 pounds, 12 ounces (3,523 grams). At 7 months of age her height was 65 cm. (average at this age 67.5 cm.). During early childhood she had had numerous attacks of purulent otitis media. At age 8 years a diagnosis of chrondrodystrophy was made. At that time she was 44½ inches tall (111 cm.: average height at 8 years, 125 cm., standard deviation, 5 cm.) and she weighed 53¼ pounds (24.2 kilograms). A note was made that she had stubby fingers. She had always been slow at school and was left back twice.

She had measles, German measles, pertussis, mumps, and chickenpox, all before she was 10 years of age. The tonsils and adenoids were removed in early childhood. Appetite, bowels, and sleep were normal. Menses began at 13 years and were regular.

On examination M. was an unusually short girl, 50 inches (125 cm.) tall. The shortness was both in the trunk and the lower extremities, the ratio of sitting height to total body height being normal for her age. The arms were unusually short. The arm span was less than the total body height, the reverse of what is normally seen. The head was normal in size (circumference, 50 cm.) and rounded. The face was broad and the base of the nose depressed with prominent nostrils. The neck was relatively short and so were the arms. The hands were short and broad and the fingers irregular in length. Similar irregularities in length were present in the toes. The joints were freely movable.

Her intelligence was in the low normal range (Wechsler-Bellevue score, 86). The Rorschach examination indicated a docile, immature personality. The right pupil was slightly larger than the left; both reacted to light and convergence. There were no lenticular opacities. On tapping either facial nerve near the angle of the jaw, there was a sharp contraction of the corner of the mouth, the alae nasi, and the corner of the eye (positive Chvostek sign). The jaw jerk was not elicited. The cranial nerves were otherwise negative. Sensation was intact. The Trousseau sign was negative. The muscles were firmer than usual and there was diminution in the quantity of subcutaneous fat. The deep reflexes were equal and diminished throughout.

The red and white blood-cell counts and the hemoglobin were normal. The urinalysis was negative. Spinal fluid was normal (calcium 4.7 mg. per 100 c.c.). The serum calcium was 8.4 mg. per 100 c.c., the serum inorganic phosphorus 7.0 mg., and the phosphatase 5.7 Bodansky units. At a later examination the serum calcium was 6.7 mg.

Fig. 1.—Patient M. C., showing (left) short stature, stocky build, rounded facies, and (above) prominent nostrils.

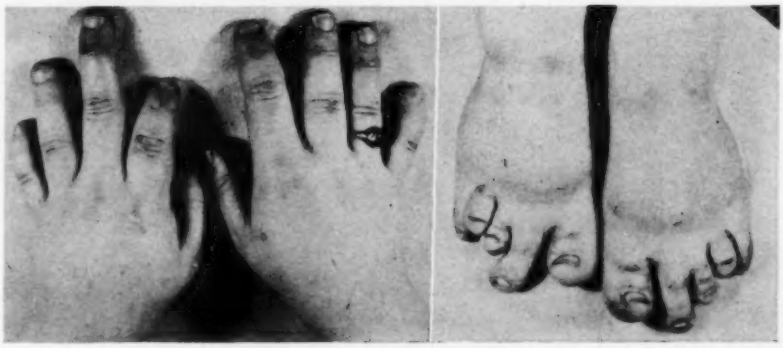

Fig. 2.—The hands and feet of M. C., showing irregularity in the lengths of the digits.

Roentgenologic Examination: (Figs. 3, 4, and 5). The skull was thickened throughout. The ulnae and radii were broad and gnarled and the fibulae were bowed inward with subperiosteal reinforcement. The pelves and hips were normal. The metacarpals were deformed with the distal ends of all except the first showing sharply demarcated areas of decreased density such as are seen in chondrodystrophy. They were short and broad with the exception of the second on the right and the third on the left. The phalanges were normal except for the first phalanx of the third finger on the left, which was long. The metatarsals

appeared to be normal except for the second metatarsals, which were unusually long. The phalanges were distorted as in chondrodystrophy. There was no premature closure of the epiphyses.

Soft tissue calcifications were not observed. Roentgenograms of the teeth revealed considerable resorption of the apices of almost all the teeth. In general there was underdevelopment of the entire dentition. The periodontal membrane was normal.

The electrocardiogram was normal.

The electroencephalogram showed a petit mal variant record. There were high voltage, 3-per-second waves, and irregular high voltage spikes without characteristic dome-spike configurations. Hyperventilation produced an immediate but moderate increase in the frequency of slow waves and spikes.

Fig. 3.—Skull, showing thickened diploe.

The response to injection of parathyroid extract was studied on two occasions. The results are shown in Table I. In neither instance was there the increase in the excretion of phosphorus in the urine and the elevation of serum calcium which one would expect in a normal individual or in a patient with true hypoparathyroidism.[3]

Shortly after these examinations were completed, M. developed typical symptoms of tetany. She had carpal and pedal spasm and generalized spasms with loss of consciousness which were temporarily relieved by the intravenous injection of 10 c.c. of 10 per cent calcium gluconate. She had been receiving 200,000 units of vitamin D_2 a day for six days. At this time she exhibited a very unusual finding. Her left hand and foot assumed a posture of spasm at a time

Fig. 4.—The roentgenologic appearance of the feet and hands. For description, see text.

when the right extremities were free of such symptoms. At the same time a Chvostek sign could be elicited on the left side but not on the right. This phenomenon of hemitetany has been observed in human subjects[4] and has been duplicated in animals. In dogs rendered tetanic by extirpation of the parathyroids, ablation of the frontal cortex on one side was associated with an increase in tetanic signs on the opposite side of the body.[4]

The patient was given daily doses of 10 drops of dihydrotachysterol. After two months the symptoms and signs of tetany had disappeared. The serum calcium was 10.2 mg. per 100 c.c. and the inorganic phosphorus 3.0 mg. The daily dosage was then reduced to 5 drops of dihydrotachysterol; later calciferol, 100,000 units daily, was given instead.

Fig. 5.—Gnarled appearance of the radius and ulna.

COMMENT

A total of nine cases of pseudohypoparathyroidism, including our own, have been reported, three by Albright and his associates,[1] one each by Sprague, Harris, and Power,[5] Peterman and Garvey,[6] Alexander and Tucker,[7] and two by Selye.[8] Albright and Reifenstein[2] mention that they have observed an additional case.

Though most of the patients have not come under observation until they were adults, the earliest manifestations appear, as a rule, in childhood. The age at which the first symptoms were noted in the reported cases varied from 9 months to 14 years.

The clinical picture of pseudohypoparathyroidism is distinctive. The diagnosis can be made with a fair degree of certainty on the clinical features alone. These are: (1) the symptoms and signs of tetany: convulsions, carpopedal spasm, laryngeal spasm, positive Chvostek and Trousseau sign; (2) alterations in body configuration reminescent of, but not typical of achondroplasia: short stature, sturdy build, rounded features, irregularities in the lengths of metacarpals and metatarsals; and (3) areas of calcification in the soft tissues.

The body build characteristics of the patients with pseudohypoparathyroidism resemble in many respects those observed in achondroplasia. The patients

are short and broad, the faces are rounded, and the extremities are short. X-rays of our patient showed the gnarled appearance of the forearn bones characteristic of achondroplasia. In addition the distal portions of the metacarpals showed sharply demarcated light areas such as are seen in the bones of achondroplastic dwarfs. In the feet, too, the changes in the phalanges resemble those of achondroplasia. Irregularity in the lengths of the fingers (and sometimes the toes) is a distinctive feature of the syndrome.

Albright and Reifenstein[2] mention that calcification of the soft tissues appears to be a more prominent feature of pseudohypoparathyroidism than of true hypoparathyroidism. One of their patients showed numerous areas of soft tissue calcification in the extremities and another showed similar areas in the soft tissues of the chest, abdomen, and extremities, some of which were palpable. Three other patients showed soft tissue calcifications. Two of these, in addition, had intracranial calcifications.

A patient recently reported by Scott and Temple[9] under the title "Osteoma Cutis" may belong to this group. The patient, a mentally retarded boy aged 9 years, had shown abnormalities of growth since early infancy. At 5 months, he was unusually large, he weighed 14.8 kilograms, and was 73.7 cm. tall. At 2 months a vesicular rash appeared on the right thigh which spread rapidly, involving the extremities and abdomen. The rash formed hard, rough, nontender lesions, the largest of which was an area in the right thigh, approximately 2 × 4 cm. At this time the serum calcium was normal (10.1 mg.). A diagnosis of obesity and scleroderma was made.

At about 2 years he began to have convulsions. At 9 years he was admitted because of otitis media and hard discrete masses beneath the skin. They were distributed over the entire body but were especially numerous in the right groin and just superior to the right malleolus. The boy was obese and was retarded in his school work. Roentgenograms revealed small areas of calcification in the

TABLE I.

TIME	PHOSPHORUS IN URINE (MG./HR.)	SERUM CALCIUM (MG./100 C.C.)	SERUM PHOSPHORUS (MG./100 C.C.)
		First Test	
8 A.M.		8.1	6.9
8-9 A.M.	17.3		
9-10 A.M.	18.5		
10 A.M.	200 units of parathyroid extract (Lilly) intravenously		
10-11 A.M.	10.8		
11-12 Noon	10.8		
12 Noon		8.8	6.8
		Second Test	
11 A.M.		6.7	7.5
7-11 A.M.	25.8		
11-12 Noon	12.0		
12 Noon	200 units of parathyroid extract (Lilly) intravenously		
12-1 P.M.	13.8		
1-2 P.M.	13.6		
2 P.M.		6.6	7.3

Table I shows the reaction of M. C. to the injection of parathyroid extract. There is no increase in the urinary output of phosphorus or elevation in the serum calcium as one would expect in true hypoparathyroidism.

region of the right thigh and right ankle. Biopsy showed that these areas consisted of true bone. The serum calcium was 7.1 mg., the serum phosphorus 13.1 mg. The alkaline phosphatase was 8.0 Bodansky units. At a later examination the serum calcium was 9.1 mg., the phosphorus 9.4, and the phosphatase 15.4 units.

In patients in whom the presenting symptom is calcification of the soft tissues, therefore, the possibility of pseudohypoparathyroidism should be considered.

It is of interest that abnormalities in the hands and feet are frequently observed in patients with another disease of calcium metabolism, myositis ossificans progressiva. Malformations of the great toe were first mentioned by Helferich in 1877[10] and since then microdactylia has been observed in about two-thirds of the cases.[11] Patients with myositis ossificans, however, show no hypocalcemia and none of the other clinical manifestations of pseudohypoparathyroidism.

Our patient had the electroencephalographic changes characteristic of "petit mal variant".[12] One of Albright's patients showed the electroencephelogram changes of epilepsy. Peterman's and Garvey's patient showed 6-per-second waves and a big build-up on hyperventilation with 3-per-second waves. The tracings were not considered characteristic of epilepsy.

A curious feature of this strange disease is the mental status. Though none of the patients was grossly defective, several were of borderline intelligence. Our patient was definitely slow in her work at school. Her I. Q. was 86. A survey of approximately 1,000 patients at the Craig Colony for epilepties at Sonyea, N. Y., where patients with severe mental defect are housed, failed to reveal any with the characteristic hand changes of pseudohypoparathyroidism.

According to Albright and his associates[1] the characteristic changes in the blood are reduction in the serum calcium and elevation of the inorganic phosphorus, the alkaline phosphatase remaining unchanged. It is of interest that the serum calcium level of our patient at the first examination was 8.4 mg. This is an abnormally low value but it is higher than that ordinarily seen in patients with tetany. At a later examination the serum calcium was 6.7 mg. Scott's and Temple's patient with osteoma cutis also showed spontaneous variations in the serum calcium. One examination gave a value of 7.1 mg.; later the level was 9.1 mg.

The finding of a serum calcium above 8 mg. per 100 c.c. is therefore not incompatible with the diagnosis of pseudohypoparathyroidism. Apparently spontaneous fluctuations in the serum calcium take place and repeated determinations are necessary. The serum inorganic phosphorus, though generally elevated, also shows considerable variation.

The distinctive metabolic alteration in patients with pseudohypoparathroidism is the failure to respond to injections of parathyroid extracts with an increase in the urinary output of phosphorus and an elevation of the serum calcium as do normal individuals and patients with true hypoparathyroidism. It is this feature which led Albright to conclude that the metabolic defect is an insensitivity of the receptors to parathormone. He dismissed the possibility of an

"anti-hormone" because none of his patients had previously received parathormone and there was, consequently, no opportunity for the development of inhibiting substances. He proposed the term "Seabright Bantam Syndrome" because, in that breed, the rooster fails to develop male characteristics owing to a failure of the end organs to respond to male sex hormone.

Albright and his associates[1] observed that patients with this syndrome respond to dihydrotachysterol (At-10) more slowly than do patients with true hypoparathyroidism, and this has been the general experience. In the patient described by Sprague, Harris, and Power[5] calciferol seemed to be as effective as AT-10. According to Albright and his associates,[13] vitamin D and AT-10 have a double effect. They increase calcium absorption from the intestinal tract and, at the same time, they increase the excretion of phosphate by the kidney. The proportion of these effects, one to the other, however, differs with the two agents. With AT-10 the ratio of the phosphorus excreting effect to the calcium absorption effect is greater than with vitamin D. Alexander and Garvey suggest that the mechanism for phosphorus excretion in the urine is at fault in pseudohypoparathyroidism; hence vitamin D, which has greater calcium absorbing action, is, theoretically at least, more effective than AT-10.

It would appear, therefore, that the treatment of choice for patients with pseudohypoparathyroidism is vitamin D combined with oral calcium. This seems to be as effective as AT-10 and it is cheaper.

SUMMARY

1. A girl, 16 years old, with pseudohypoparathyroidism is reported.

2. Nine patients with this condition have been reported.

3. The distinctive clinical features are: (1) the signs and symptoms of tetany, (2) characteristic alterations in body configuration. The subjects are short and stocky, the facies are rounded, and there are abnormalities in the lengths of the finger bones and often of the bones of the feet, and (3) soft tissue calcifications.

4. The serum calcium is reduced and the inorganic phosphate elevated.

5. The patients fail to respond to parathormone like normal or hypoparathyroid individuals with an increase in the excretion of phosphorus in the urine and an elevation of the serum calcium.

6. Dihydrotachysterol acts more slowly in patients with this disease than in those with true hypoparathyroidism.

7. The treatment of choice is with vitamin D in high doses combined with orally administered calcium.

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ELECTROENCEPHALOGRAPHIC FINDINGS IN MEASLES ENCEPHALITIS

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APPROXIMATELY one child in 1,200 suffering from measles develops detectable evidence of encephalitis. Fortunately, the great majority of such children recover completely from an attack of measles encephalitis, but a certain number of individuals do have sequelae of varying degrees of severity. The possibility of permanent injury to the central nervous system is, therefore, present in each case of measles encephalitis, and any method which might give a clue to the ultimate prognosis would be of great value. With this idea in mind we have made electroencephalographic studies of eight children at various intervals following the onset of measles encephalitis and of six children with uncomplicated measles.

The electroencephalograms were taken on the patients with encephalitis during or very soon after the acute stage of the encephalitic symptoms, and the progress of each patient was followed with serial electroencephalograms. The electroencephalograms were taken on the six patients with uncomplicated measles between the ninth and twelfth day after the onset of the measles, since this is the time these patients would be most likely to develop measles encephalitis.

The ages of the patients varied from 5 to 10 years. There was no history of previous convulsive disorders nor was there any family history of convulsions or epilepsy.

All of the eight patients with encephalitis in the acute stage showed quite similar electroencephalographic abnormalities consisting of abnormally slow high voltage waves, whereas the patients with the uncomplicated measles presented normal electroencephalograms.

CASE REPORTS

For the purpose of this discussion the case histories and the electroencephalographic tracings of three exemplary patients are presented below. A four-channel Offner electroencephalograph was used to perform the tests. All of the tracings shown in Figs. 1 to 8 are monopolar (scalp-to-ear) leads taken during the resting state. Bipolar (scalp-to-scalp) tracings were also obtained in each case, and the changes were found to be essentially the same as with the scalp-to-ear leads.

CASE 1.—S. M., an 8-year-old white child, appeared to be convalescing normally following measles until the seventh day after onset. At this time she began to complain of headache, vomited several times, and had a series of convulsions over a fourteen-hour period. She was delirious on admission to the hospital and became comatose soon after. Forty-eight hours after onset of symptoms of encephalitis she regained consciousness and except for noticeable apathy seemed to be nearly normal. By the third day after onset she seemed quite normal; she was alert, cheerful, and quite clear mentally. On the fourth

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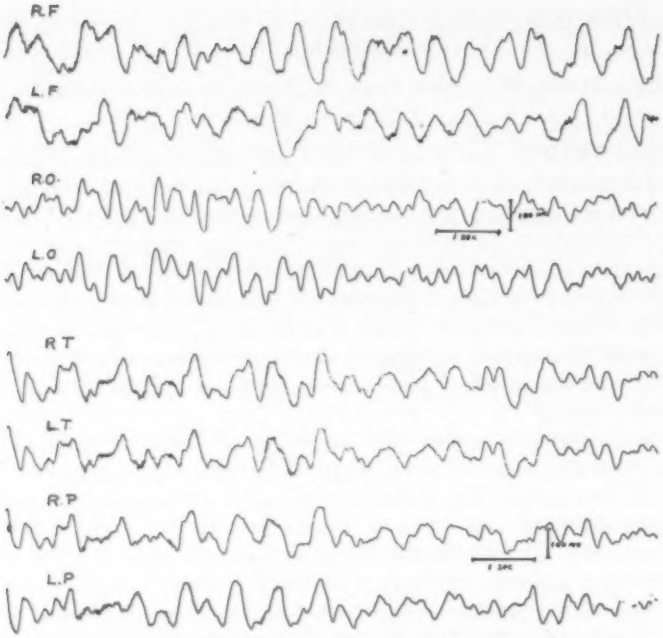

Fig. 1.—Electroencephalogram of S. M. taken four days after onset of measles encephalitis. The patient was well clinically.

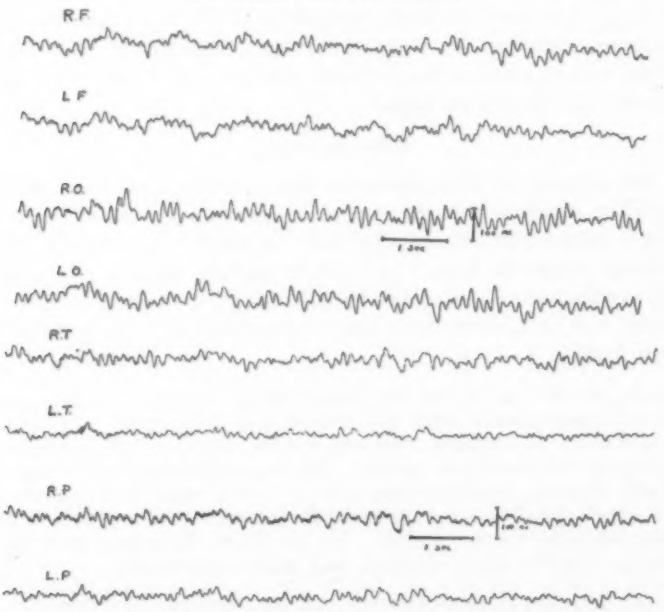

Fig. 2.—Electroencephalogram of S. M. taken twenty days after encephalitis. The patient was well clinically.

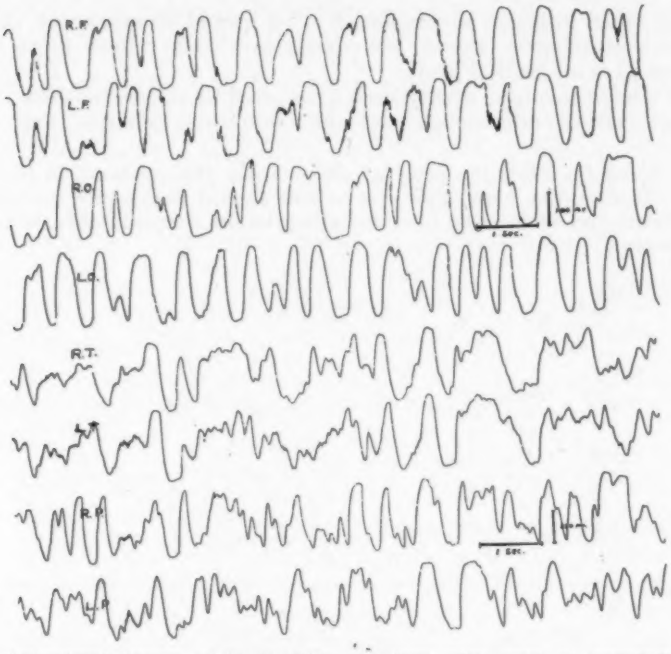

Fig. 3.—Electroencephalogram of B. S. taken five days after onset of encephalitis. The patient was stuporous.

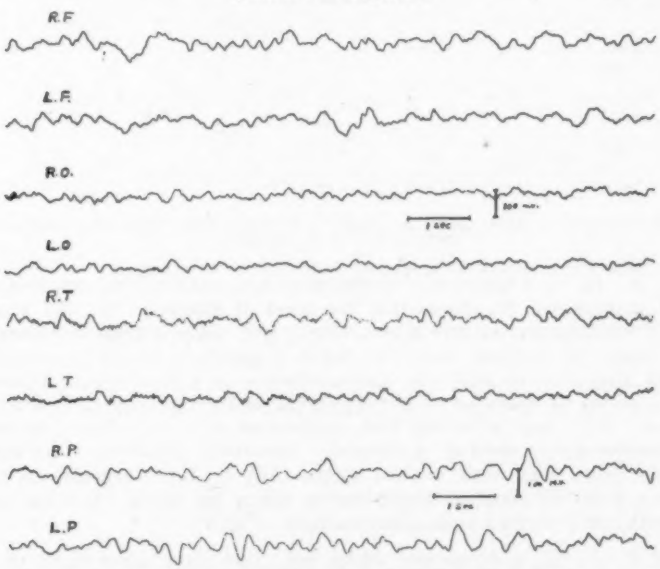

Fig. 4.—Electroencephalogram of B. S. taken six weeks later (a few days before death). The patient was in a semistuporous state.

day after onset, although she appeared to be normal in every way clinically, an electroencephalogram showed abnormally slow high voltage waves (1½ to 2 per second) in all leads (Fig. 1).

She was re-examined twenty days after onset of the encephalitis. At this time the physical examination and the electroencephalogram were normal (Fig. 2).

Seven months after the onset of encephalitis, she appeared to be entirely normal. It should be noted that this patient seemed to be quite well clinically on the fourth day after onset of encephalitis despite a grossly abnormal electroencephalogram.

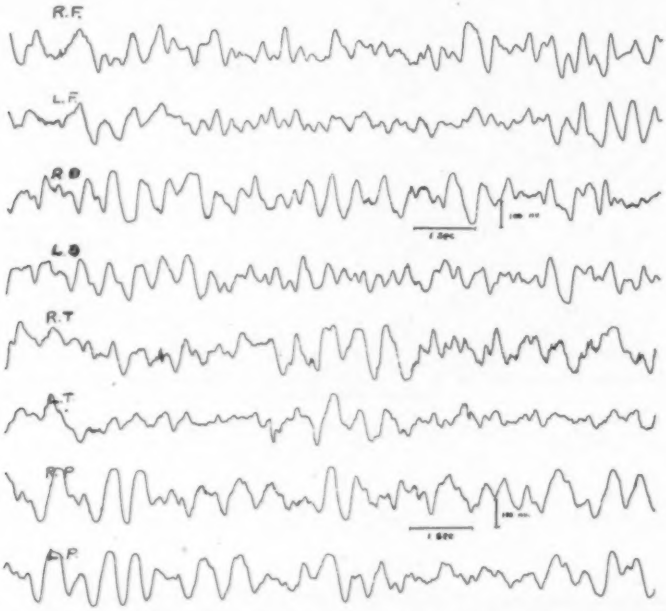

Fig. 5.—Electroencephalogram of F. H. taken four days after onset of encephalitis. The patient was well clinically.

CASE 2.—B. S., a white boy 10 years of age, suffered an extremely severe attack of encephalitis six days after the onset of measles. He had a series of protracted convulsions, lapsed into a coma, and never regained consciousness. He was unable to swallow, had very marked paralysis of all extremities, and eventually appeared to have the characteristics of a decerebrate animal. He suffered a series of episodes of hyperpyrexia and eventually died seven weeks after onset. Five days after the first appearance of encephalitic symptoms, his electroencephalogram showed a severely abnormal brain-wave pattern with abnormally slow, very high voltage waves (1½ to 2 per second) in all leads (Fig. 3). A repeat electroencephalogram taken six weeks later (a few days before death) still showed gross abnormalities (Fig. 4).

CASE 3.—F. H., a 6-year-old white boy, four days after onset of coryzal symptoms of measles, began to have severe convulsions. Three days later he developed definite signs of measles encephalitis. An electroencephalogram taken four days after onset of encephalitic symptoms, at which time he seemed to be

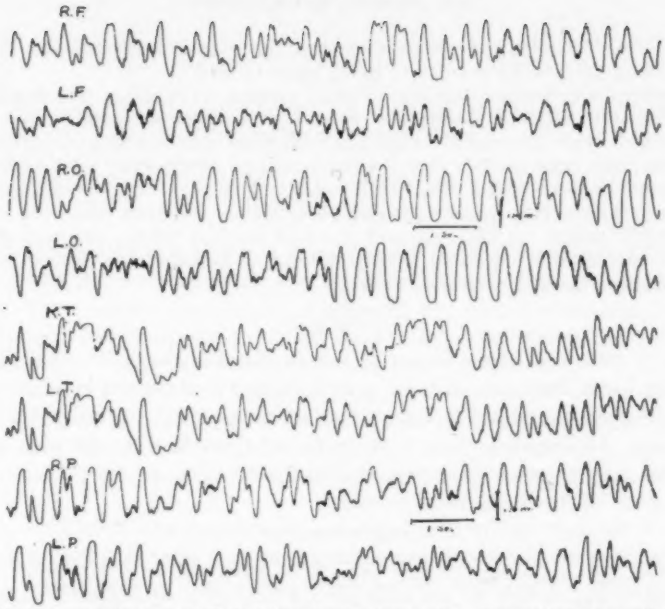

Fig. 6.—Electroencephalogram of F. H. taken twelve days later. The patient was well clinically.

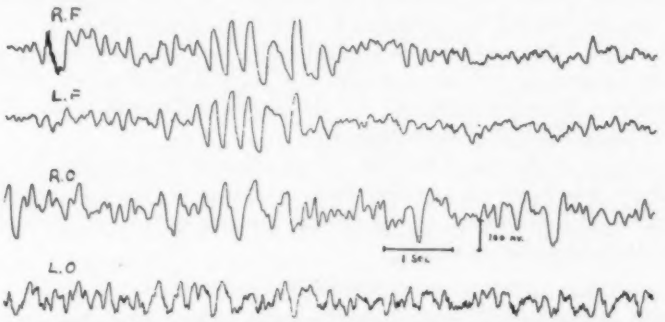

Fig. 7.—Electroencephalogram of F. H. taken fifty-three days later. The patient was well clinically.

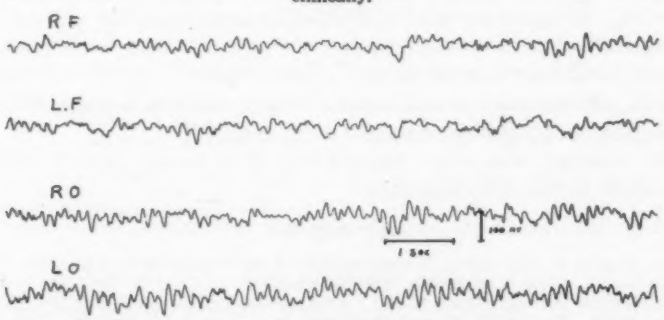

Fig 8.—Electroencephalogram of F. H. taken two and one-half months later. The patient was well clinically.

entirely well clinically, showed an abnormal pattern with abnormally slow high voltage waves (1½ to 2 per second) in all leads (Fig. 5).

A repeat electroencephalogram taken sixteen days after the onset of the encephalitis still showed abnormally slow high voltage waves although the patient seemed well clinically (Fig. 6). Another electroencephalogram taken fifty-three days later showed paroxysmal bursts of abnormally slow high voltage 3-per-second waves during the resting state (Fig. 7). There was also a tremendous build-up with hyperventilation and a slow recovery following cessation of hyperventilation. About two and one-half months later (150 days after the onset of encephalitis) reexamination showed a normal electroencephalogram, and the patient seemed to be well (Fig. 8).

COMMENT

As has been previously shown by others (Lindsley and Cutts,[1] Ross,[2] Gibbs and Gibbs,[3] and Shinners, Krauss, and Rochester[4]) abnormal electroencephalographic findings are found in many types of encephalitis, including that following measles. Our examinations have confirmed these findings and also indicated that serial electroencephalographic studies are of value in reaching conclusions regarding the ultimate degree of recovery.

All of the eight children with measles encephalitis who were studied showed markedly abnormal electroencephalograms at or soon after the onset of symptoms of encephalitis. The abnormalities were generalized in each case. Seven of these eight children showed progressive improvement clinically and eventually showed normal electroencephalographic tracings. It is of interest to note that in each instance clinical improvement preceded the improvement in the electroencephalograph. The eighth child studied had a very severe attack of encephalitis following measles and never showed any marked improvement of his severe central nervous system symptoms. An electroencephalograph taken a few days before his death was still grossly abnormal.

In contrast to the above findings, six children of ages similar to those described above, who were convalescent from an attack of measles unaccompanied by symptoms of involvement of the central nervous system, all showed normal electroencephalographic tracings.

SUMMARY

1. All of the eight patients with measles encephalitis showed abnormal electroencephalographic findings soon after onset of their central nervous system disease. (*A*) In seven of these the electroencephalographic pattern became normal, and all of these children appear to have recovered without detectable evidence of permanent central nervous system injury. (*B*) In the case of the eighth child, the central nervous system damage did not improve, the electroencephalogram remained abnormal, and death resulted.

2. Six children who were convalescent from uncomplicated measles all showed normal electroencephalograms.

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A STUDY OF THE Q-T_c INTERVAL IN THE ELECTROCARDIOGRAM IN RHEUMATIC FEVER

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ELECTROCARDIOGRAPHIC changes indicative of myocardial disturbances are frequently but not invariably found in children with active rheumatic carditis. These consist primarily of changes in the auriculoventricular conduction time, the ventricular complex, and the rhythm. Recent studies by Taran,[1] Abrahams,[2] and others have indicated that prolongation of the Q-T_c interval offers significant additional electrocardiographic evidence of active rheumatic carditis. It, therefore, seemed of interest to analyze a series of electrocardiograms from children during one or more episodes of active rheumatic carditis. Tracings taken from the same children during periods of quiescence were also studied.

METHOD AND MATERIALS

The upper limit of the normal Q-T_c in children as given by Ashman[3] is 0.405 second. This was confirmed by an analysis of 928 tracings in normal infants and children.[4] In the present study a Q-T_c interval of 0.41 second or more was considered abnormal. Goldberger's "Q-T ratio" of 1.01[5] corresponds to a Q-T interval of 0.405 second. We have calculated this ratio in the tracings of our patients for comparison with his study.

The records of 55 children who were under medical supervision on the pavilions of The New York Hospital or in the Pediatric Cardiac Clinic were reviewed and the electrocardiograms analyzed. There were 29 boys and 26 girls ranging in age from 9 months to 18 years. The records covered a period of 162 patient years; there were 86 patient-years of active rheumatic carditis and 76 inactive years. A total of 325 electrocardiograms* were reviewed, 229 taken of children during an active phase of the disease and 96 from an inactive period.

All children experienced one or more attacks of active carditis,† with or without other manifestations of rheumatic activity. There were 58 episodes of polyarthritis with carditis, 12 episodes of chorea with carditis, and 16 episodes of carditis alone as the major manifestations of rheumatic activity. There were 28 episodes with a varying degree of congestive failure and 13 deaths. The records were evaluated clinically and the severity of the carditis was graded

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*The electrocardiograms taken while patients were receiving digitalis medication were excluded from study.

†The criteria for active carditis were:

1. Diminished cardiac reserve as manifested by dyspnea, orthopnea, and a drop in vital capacity.
2. Changes in heart size and fresh murmurs.
3. Electrocardiographic abnormalities hitherto not present.

The diagnosis of inactive rheumatic heart disease was made in the absence of all signs and symptoms, including a normal cardiac reserve.

on the basis of 1 to 4-plus. There were 24 episodes characterized as 1-plus, 29 and 16 episodes characterized as 2-plus and 3-plus respectively, and 17 episodes characterized as 4-plus.

Electrocardiograms were taken in the routine manner. The cycle length and the Q-T interval were measured in the three limb leads using all readable cycles. The average cycle length and Q-T interval were then determined and the Q-T interval corrected for rate according to the formula of Bazett: $Q\text{-}T_c = \frac{\text{Q-T in seconds}}{\sqrt{\text{R-R in seconds}}}$ where R-R = cycle length.[6] The $Q\text{-}T_c$ was also compared with the "ideal" Q-T, using the nomogram of Pokress and Goldberger.[7] The ratio of systole to diastole or $\frac{\text{Q-T}}{\text{T-Q}}$ ratio was also determined according to the method of Taran.[1, 8]

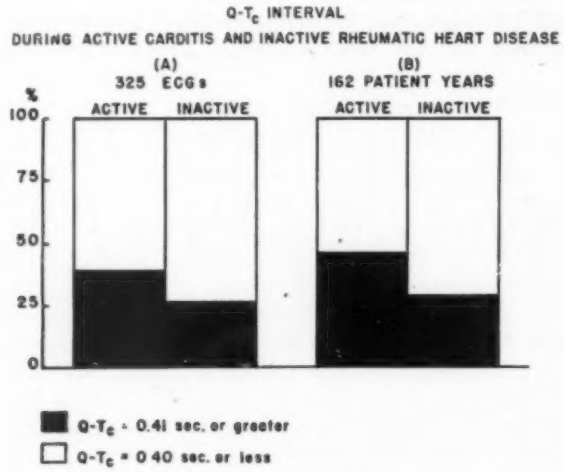

Chart 1.—A comparison of the $Q\text{-}T_c$ interval (*A*) based on total electrocardiograms, and (*B*) based on electrocardiograms per patient-years.

OBSERVATIONS

It may be seen (Charts 1 and 2) that the corrected Q-T interval was 0.41 second or more in 38 per cent of the electrocardiograms taken from patients with active carditis. In the same patients during inactive rheumatic heart disease, the $Q\text{-}T_c$ was elevated in 27 per cent. The highest $Q\text{-}T_c$ interval during an episode of rheumatic carditis was compared with the highest $Q\text{-}T_c$ interval found (in the same patient) during quiescence. The interval was 0.41 second or more in 47 per cent of the active episodes in contrast to 29 per cent during quiescent periods.

It is of interest that when the highest $Q\text{-}T_c$ interval during an active episode was correlated with severity of illness by clinical appraisal, the $Q\text{-}T_c$ interval was elevated in the electrocardiograms of 25 per cent of the patients

with 1-plus severity; in patients with 2-plus to 3-plus severity it was elevated in 47 per cent and 37 per cent respectively. The Q-T_c was elevated in the electrocardiograms of 76 per cent of those patients who experienced pancarditis and failure.

The ratio of the measured Q-T to the "ideal" Q-T interval was determined in all of the electrocardiograms studied using Goldberger's nomogram. A ratio of 1.01 or above was found in 45 per cent of the observations made during activity in contrast to 34 per cent of the observations made during the quiescent stages.

The $\frac{\text{Q-T}}{\text{T-Q}}$ ratio was determined in all tracings taken during forty-five episodes of active carditis and contrasted with the ratio obtained during a period of quiescence in the same patient. The highest $\frac{\text{Q-T}}{\text{T-Q}}$ ratio obtained in any one episode was used as a basis for comparison. It was found that the ratio was increased in 51 per cent of the active phases. The ratio was higher in the inactive phases in 22 per cent and remained the same in 27 per cent of the patients studied.

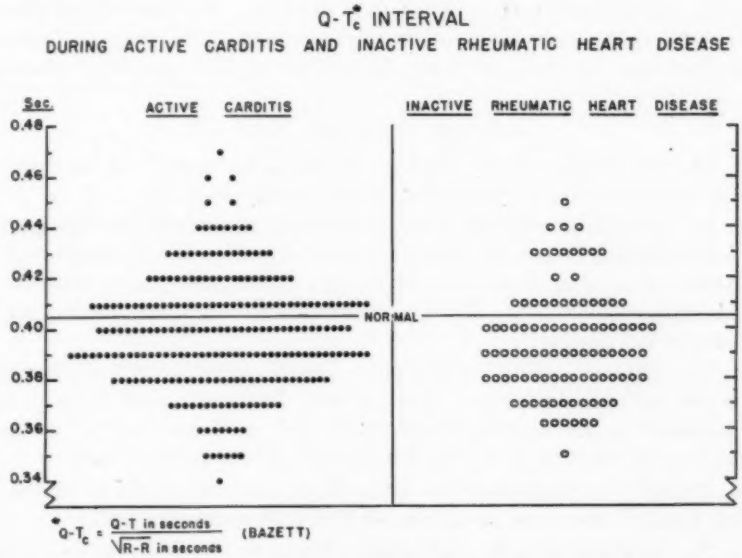

Chart 2.—A comparison of the Q-T_c interval in 325 electrocardiograms, 229 during active carditis, and 96 during the inactive phase.

COMMENT

Electrocardiographic changes, varying in incidence, are reported in active carditis depending upon the frequency with which tracings are made. The average number of electrocardiograms per patient taken during active carditis in this series was four, and inactive rheumatic heart disease, two. The patients

with inactive heart disease were free of any evidence of active carditis for periods of months to years. In our series, electrocardiographic abnormalities, exclusive of prolongation of the Q-T_c, were found in 54 per cent of the serial electrocardiograms taken during active episodes; 30 per cent of these consisted of prolongation of the P-R interval. It is significant that the incidence of prolongation of the Q-T_c interval in this series is of the same order as the incidence of accepted electrocardiographic evidence of a myocardial disturbance.

We were unable to confirm Taran's[1] observation that the duration of the Q-T_c is significantly prolonged in all cases of carditis. It was, however, significantly prolonged in the majority of our patients who experienced pancarditis or congestive failure. The Q-T_c interval was prolonged in one or more of the tracings taken during 47 per cent of the active patient years compared to 29 per cent during inactive patient years. It is of interest to note that 50 per cent of the patients with marked cardiac hypertrophy who were in apparent health had prolongation of the Q-T_c interval. The occurrence of a prolonged Q-T_c interval in patients with hypertrophy of the heart has been reported.[2]

Our results indicate that the accepted electrocardiographic criteria of active carditis are found in approximately the same percentage of patients with active rheumatic carditis as elevation of the Q-T_c interval. The observation that elevation of the Q-T_c occurs in approximately one-third of the patients during inactive rheumatic heart disease limits its usefulness as a significant diagnostic sign.

SUMMARY AND CONCLUSIONS

1. The significance of prolongation of the Q-T_c interval as electrocardiographic evidence of active rheumatic carditis was studied.

2. The interval was measured in 325 tracings taken from fifty-five patients with active carditis or inactive rheumatic heart disease. The Q-T_c interval was 0.41 second or more in 38 per cent of the 229 electrocardiograms taken during active carditis compared with 27 per cent of the 96 tracings taken during inactive rheumatic heart disease.

3. The fifty-five patients were followed for a period of 162 patient-years; 86 (53 per cent) of which were active periods. Prolongation of the Q-T_c interval was found in the electrocardiograms studied in 47 per cent of the active patient-years in contrast to 29 per cent during inactive patient-years.

4. The Q-T_c interval was elevated in the electrocardiograms of 76 per cent of those patients who experienced pancarditis with congestive failure.

5. The incidence of Q-T_c prolongation found in this study was no greater than the incidence of accepted abnormal electrocardiographic evidence of active carditis.

Prolongation of the Q-T_c interval in the electrocardiogram per se is not diagnostic of active rheumatic carditis.

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A NATURALLY FORTIFIED MILK MODIFIER

I. Laboratory Studies of Apple Syrup as a Carbohydrate for Infant Feeding

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MOST of the carbohydrate modifiers which have proved successful for artificial infant feeding have been dextrin-maltose-dextrose mixtures derived from cornstarch, though sucrose, molasses, beta-lactose, and honey have also been satisfactory. On theoretical grounds it has seemed likely that apple syrup might also be of value for this purpose, and perhaps even possess certain advantages in special situations, but such a product has hitherto not been available for this purpose.

Apple syrup is concentrated apple juice. It contains (a) three natural sugars, fructose, glucose, and sucrose; (b) minerals, of which iron seems most important; (c) vitamins, especially vitamin C; and (d) pectin, in varying but small amounts. This paper reports the results of a series of laboratory studies designed to explore the value of apple syrup as a carbohydrate modifier for infant feeding.

The apple syrup used in these studies was produced by evaporation of fresh apple juice, pressed from apples until the specific gravity was about 1.35. To minimize destruction of the substance contained in the syrup, the evaporation was performed under vacuum at relatively low temperature (140° F.). With this processing the only components lost in appreciable volume are water and aromatic substances. The syrup has been prepared from winter variety apples such as York, Jonathan, and Stayman. These varieties have a high sugar content.

Raw apple juice is a biological derivative and as such is subject to spontaneous fluctuation in chemical and physical properties. The species, year of the crop, geographical origin, and other related factors are all reflected in the composition of the product. In addition, the syrup during its preparation is subjected to vacuum distillation, enzymatic depectinization, chemical neutralization, and heat pasteurization—processes which in themselves may vary from time to time, but which also (especially the neutralization) can exert positive influence toward maintenance of uniformity. It has been our observation over an eight-year period that successive batches of syrup have exhibited only comparatively minor differences from one to another despite these variables, even with respect to flavor.

Investigations on the possible utility of apple syrup as a carbohydrate modifier for infant feeding have been in progress since 1941. Studies have been carried out with respect to the pertinent chemistry of this processed syrup, the effects of added syrup upon the curd-forming properties of milk, and clinical phenomena associated with feeding trials with infants.*

From the Milk Research Laboratory of the Children's Hospital of Philadelphia.

*Prior to 1949, batches of syrup were supplied annually by Ridgewood Fruit Industries, Inc., through Dr. Huston St. Clair (apple syrup R). The more recent investigations have been carried out with an essentially identical product, "Infose," supplied by The Borden Company (apple syrup B).

LABORATORY INVESTIGATIONS

Neutralization Experiments.—Apple syrup as it comes from the evaporating tank is somewhat acid, with a pH value ranging from 3.4 to 3.7. If added to milk in this form in from 5 to 10 per cent concentration, as is customary in infant feeding, spontaneous coagulation will often take place when the milk mixture is later heated or boiled.

It has been found that this susceptibility to coagulation can be eliminated if the pH value of the apple syrup is changed to about 5 (4.8 to 5.2) by some means of partial neutralization. The addition of concentrated (42 per cent) sodium hydroxide solution, of which only a few millimeters are needed per 100 ml. of apple juice, has been found to achieve this desired result most effectively. The amount of alkali to be added must be determined separately for each batch of syrup. The neutralization makes the syrup less acidic and darkens the color, but does not alter the flavor significantly.

The term "apple syrup" in this report refers to such partly neutralized apple syrup (pH of about 5.0).

Chemical Determination.—1. The iron content calculated from four different batches of apple syrup R tested in successive years was rather uniformly constant. Two batches of syrup B from different sources exhibited more variation.

SYRUP	SPECIMEN NO.	DATE	MG. PER 100 C.C.
Syrup R.	1	Nov., 1943	9
	2	Oct., 1944	10
	3	Oct., 1945	9
	4	Feb., 1946	9.8
Syrup B.	1	Dec., 1948	7.5
	2	April, 1949	15.6

The content of iron of apple syrup may accordingly be stated in general to fall in the neighborhood of 10 mg. per 100 c.c.

2. The pectin content of successive batches of apple syrup has ranged between 0.02 per cent and 0.5 per cent. In these concentrations the pectin content does not interfere with the solubility of the syrup in milk, even at refrigerator temperatures. Only when the pectin content has been artificially increased more than from 3 to 4 per cent will a decrease in solubility become noticeable. The amount of pectin in apple syrup B has been standardized at approximately 0.5 per cent by the addition of measured amounts. Pectin physiologically favors intestinal motility and absorbs some bacterial toxins.[1, 2] The percentage incorporated in apple syrup has been arrived at by a series of clinical trials.

3. Analysis of a representative sample of syrup in a specific gravity of 1.35088 (70° Brix or 38.1° Baumé) showed the contained sugars to be distributed in the following amount and proportions:

Levulose	33.3%	Total solids	69.8%
Dextrose	12.6%	Water	30.2%
Sucrose	12.6%		100.0%
Total sugars	58.5%		

These values show little deviation from batch to batch. The relatively high levulose content accounts for the sweet taste of apple syrup.

4. The thiamin content was low, being 0.8 μg in 100 Gm. of one specimen of syrup. A single test for vitamin A gave a negative result.

5. The vitamin C content was studied most intensively in syrup R. In fresh batches, vitamin C was present in considerable amounts, about 30 mg. per 100 ml. apple syrup. Successive samples were tested over a period of eight months, some being stored at room temperature and others in a refrigerator at about 45° F. (Table I.)

TABLE I. LOSS OF VITAMIN C DURING STORAGE OVER EIGHT-MONTH PERIOD (SYRUP R)

	MG. PER CENT VITAMIN C DURING STORAGE AT	
	REFRIGERATOR TEMPERATURE	ROOM TEMPERATURE
Jan., 1944	29.2	29.2
April, 1944	26.5	24.5
Aug., 1944	22.4	19.5
Actual loss (mg.%)	6.8	9.7
Percentage of loss	23.3	33.2

About one-fourth of the natural vitamin C content was lost during storage at refrigerator temperature, and about one-third was lost during storage at room temperature from January until August, 1944. Vitamin C concentration was determined by titration with 2.6 dichlorphenol indophenol.

In a further study the apple syrup was fortified with vitamin C. Ascorbic acid (200 mg.) was added to each bottle of 360 ml. of apple syrup (12 ounces). This would provide 30 mg. ascorbic acid per day, the minimum required for protection against vitamin C deficiency, if from 1½ to 2 ounces, or about 50 ml. apple syrup per day were being fed to an infant, and if deterioration did not occur. Tests over a period of eight months showed a rate of reduction in such fortified preparation similar to that in the unfortified syrup.

Bacteria Content.—As a rule, fruit juices are easy to keep from fermenting on account of the high acidity from natural fruit acids. It would be expected, therefore, that after prolonged evaporation of the original apple juice at a temperature of about 140° F., the yeast spores would be destroyed, and the bacteria content be low in the final product. An experiment confirming this conclusion is summarized in Table II.

TABLE II. BACTERIA CONTENT IN APPLE SYRUP R

	BACTERIA (PER ML.)	YEAST (PER ML.)	MOLD (PER ML.)
Original apple juice	2,000,000	—	present
Apple juice, filtered	120,000	300	0
Concentrated apple juice (apple syrup before canning)	4	0	0

It has been our observation that batches of pasteurized syrup will remain stable, unless contaminated with yeast or bacteria from outside sources. The flavor may however become somewhat altered if the syrup is stored for years, indicating that minor changes, probably of enzymatic origin, are taking place.

Influence Upon Curd-Forming Properties of Milk.—Addition of 5 per cent apple syrup to cow's milk, which corresponds to the proportion customary in

milk formulas, produced an approximate 10 per cent lowering of the curd tension, and about 10 per cent smaller curd size of the milk when such mixtures were tested under standardized laboratory conditions. For example, with a representative sample of pasteurized milk the curd tension was reduced from 45 Gm. to 41 Gm. by addition of 5 per cent apple syrup, and the curd number increased from 132 to 146 on the arbitrary scale. The curd tension procedure was that approved by the American Dairy Science Association,[3] and the curd size was measured by the "curd number" test described by the authors.[4] When higher concentrations of apple syrup were added, the curd modifications were somewhat more marked, but none of these were of sufficient magnitude to render such mixtures "soft curd," though the trend was in that direction.

BIOASSAY FOR AVAILABILITY OF THE IRON CONTENT

The nutritional availability of iron in apple syrup was assayed by determining its efficiency in hemoglobin regeneration in young white rats made previously anemic by an iron-free diet. Both R and B forms of apple syrup were tested, employing six sets of animals (in accordance with the technique of Ascham and co-workers.[5] The procedure consisted of: (a) a depletion period of from seven to nine weeks, during which the animals were made anemic, and (b) an assay period of from six to seven weeks in which apple syrup was fed and compared with the control feeding (positive controls) of either ferric chloride plus manganese and copper, or a normal adequate diet containing all essential minerals, including iron. In all but one of the series a negative control group of animals was present and fed an iron-free diet.

The procedure of Ascham and co-workers was followed as closely as possible. The rats were selected in equal numbers of males and females of the same litter, just weaned. At the end of the depletion period, the animals were divided as evenly as possible with respect to sex and hemoglobin level into the different testing groups and put into separate cages. In the first experiment hemoglobin tests were performed at the end of each week, but in later experiments the tests were performed at greater intervals in order to avoid possible erroneous results from too much loss of blood. The depletion diet consisted of powdered milk and distilled water, ad libitum. The hemoglobin estimations were done with the Klett colorimeter. In one series [Table III (Experiment 4)], however, red blood-

TABLE III. (EXPERIMENT 4) EFFECT OF APPLE SYRUP ON HEMOGLOBIN REGENERATION IN RATS

NUMBER OF ANIMALS	CLASSIFICATION (DIET)	AVERAGE WEIGHT GAIN (GM.)	AVERAGE HEMOGLOBIN GAIN (GM.)	AVERAGE BLOOD COUNTS AT END OF SIX WEEKS ASSAY PERIOD	AVERAGE TOTAL HEMOGLOBIN (GM. PER 100 ML. BLOOD)
6	2.5 ml. apple syrup (0.3 mg. iron)	44	7.1	8,873,000	13.6
6	1.7 ml. apple syrup (0.2 mg. iron)	34	5.2	—	—
6	Negative control	–5	0.9	4,580,000	5.8
4	Positive control	39	0.2	7,997,000	13.3
	(Gross autopsy showed no evidence of infection.)				

cell counts were performed also, in order to check on the hemoglobin values. The negative control group animals became extremely anemic, but many of them seemed able to survive indefinitely at extremely low levels of hemoglobin. Other investigators have reports that rats thus made anemic died after a certain period of time. At the end of the experiment, some of the negative control group animals were given away for breeding purposes, and both males and females proved to be sterile. Gross autopsy examinations failed to show any lesions due to infection or other diseases; the negative control group animals showed the expected pallor of all tissues.

These are the results in a typical experiment with apple syrup B:

White rats, just after weaning, were kept on a diet of distilled water and powdered milk for a period of nine weeks, until pronounced anemia had developed. The best group was chosen for positive control, the next best for negative control, and the group lowest in hemoglobin was chosen for the apple syrup group. Each group consisted of eight animals, evenly divided, as far as possible, as to males and females.

The positive control group animals received the same diet in the depletion period with the addition of a solution containing iron, copper, and manganese. Each rat received 0.3 mg. of iron as ferric chloride per day, 0.05 mg. copper as copper sulfate, and 0.04 mg. manganese as managanese sulfate.

The negative control group animals received the same diet as in the depletion period and in addition 4 ml. of corn syrup.

The apple syrup group animals received the same diet as in the depletion period with the addition of 4 ml. apple syrup, corresponding to 0.3 mg. iron per day. The assay period for all groups was seven weeks. The mean results are shown in Table IV.

TABLE IV

	GM. Hb PER 100 ML. OF BLOOD			GAIN IN GM. BODY WEIGHT DURING EXPERIMENT
	AT START	AFTER 7 WEEKS	GAIN	
Positive controls	8.4	15.4	7.0	37
Negative controls	7.1	6.6	−0.5	−10
Apple syrup group	5.9	15.1	9.2	83

These results indicate that the iron in apple syrup is nutritionally available. It is not necessary to add copper or manganese to the apple syrup to produce blood regeneration in animals.

The iron content of the corn syrup was found to be 0.26 mg. per cent, a negligible amount, compared with 7.5 mg. per cent in the apple syrup B used for this experiment. The weight gain, and notably the hemoglobin gain, was negative in the corn syrup-fed negative control animals.

SUMMARY

Apple syrup has been found to be a good source of the simple sugars: levulose, dextrose, and sucrose. Its iron content (about 10 mg. per 100 c.c.) has been shown to be readily available in the correction of anemia in test animals (albino rats).

The apple syrup has been found to be stable and bacteria-free when prepared from apple juice by evaporation under vacuum at 140° F.

For use in infant feeding formulas the crude apple syrup has to be partly neutralized to a pH of about 5.0. The vitamin C content has been shown to be relatively stable, losing about 33 per cent of its strength in six months, when the apple juice is stored at room temperature, and 25 per cent when stored at refrigerator temperature. Added vitamin C shows approximately the same rate of stability.

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A NATURALLY FORTIFIED MILK MODIFIER

II. Clinical Studies of Apple Syrup as a Carbohydrate for Infant Feeding

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LABORATORY studies have indicated that partially neutralized apple syrup possesses chemical and nutritional properties which would make it a satisfactory carbohydrate supplement for use in infant feeding. The high sugar content of the syrup, the fact that it is essentially a concentrate of apple with only the pulp removed and a little sodium hydroxide added, plus the observation that rats, fed appreciable quantities of it over a period of several months, failed to exhibit any symptoms of distress or toxicity, made it seem likely that no major difficulties would be encountered in clinical usage.

The first feeding trials were conducted with a few infants and children under careful observation. Only after preliminary studies had demonstrated its safety and digestibility were more extensive feeding trials begun. Studies were carried out with two series of healthy infants being reared in institutions and at their own homes; with a series of carefully followed newborn and premature infants receiving nursery care; and with sick infants, anemic infants, older children with celiac disease, and miscellaneous other groups of infants and children. At least 600 other normal infants have been given the syrup for short periods of time. The only ones included in the following tabulations are those in whom the duration of close observation has been at least six weeks.

Normal Infants.—Series I consisted of seventy-three young infants in two nursing homes.* All were in apparent good health and of normal physical size, and were under daily medical and nursing care. When first admitted to these institutions, the seventy-three infants were given the syrup in homogenized milk, and kept on this milk mixture until discharge. The formulas consisted of homogenized pasteurized milk containing one ounce of apple syrup per 20 ounces of milk. The mixture was fed unboiled and undiluted and served on the basis of 1.5 to 2.0 ounces of milk per pound of body weight, depending on the appetite. The mean age at starting was 31 days, with range from 10 days to 3 months; the mean age at stopping was 113 days, with range from 55 days to 6 months. The mean period this formula was taken was 2.63 months. During the observation period, no solid or other food apart from the mixture of homogenized milk and apple syrup was given, except for supplements of vitamins A, C, and D.

The mean number of daily stools for the seventy-three infants was 2.5. The stools were for the most part soft, and a little darker than those usually given

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*The infants in Series I were fed apple syrup processed and supplied by Ridgewood Fruit Industries, Inc., of Winchester, Va., through Dr. Huston St. Clair. The other groups of infants and children were given an essentially similar product processed and supplied by the Prescription Products Division, The Borden Company, New York, known as "Infose."

by formulas containing modified carbohydrates derived from corn. The texture was smooth, and they contained no unusual curds. The reaction was almost invariably acid. No diarrhea developed which seemed to be due to the syrup.

Series II consisted of healthy infants attending well-baby outpatient clinics. The feedings consisted of apple syrup as the carbohydrate modifier in a variety of cow's milk preparations. Solid foods were added at about 3 months of age, in accordance with standard practice. Of these infants, twenty-five returned regularly enough to be deemed adequate for study. The mean age at starting was 2.3 months, with range from 4 weeks to 5 months; the mean age at stopping was 5.4 months, with range from 2½ to 8½ months. The mean duration of taking apple syrup was 2.7 months, with range from one to seven months. The hemoglobin levels of these infants were determined at regular intervals, along with height and weight measurements. Forty other infants from the same population, observed during the same period, were taken as control group infants; these were being reared on breast milk or on artificial feedings made up with corn syrup. The mean growth curves and the mean hemoglobin levels for the two groups ran approximately parallel. Records for diarrhea, constipation, and regurgitation submitted by the mothers showed no essential differences between the two groups.

No difficulty was encountered in preparing or feeding the formulas with either group of infants. Transient vomiting associated with the first introduction of the syrup was noted in eleven instances. This was not persistent and did not necessitate stopping the syrup. Regurgitation of small amounts was no greater than with infants receiving other carbohydrates.[1] No rashes of eczematous or allergic nature were encountered in this series or in any of the other groups of infants which could be etiologically attributed to sensitivity to apple.

Newborn and Premature Infants.—The apple syrup was used as the carbohydrate modifier in the feeding of 105 newborn infants, commencing on the first or second day of life. The milk mixtures were made of diluted evaporated milk, with apple syrup added in concentration of 5 to 10 per cent by volume of total mixture. Of these infants, eighty-one were in a maternity hospital nursery. They received these feedings until discharge from the nursery, usually at the age of 7 or 8 days. Most were given this mixture as the sole source of nutriment, but a few received also a little mother's milk by nursing at the breast. The feedings were well taken and well tolerated. One newborn infant in this group of 105 exhibited loose stools and was taken out of the study on the fifth day.

Twenty-four infants were at a nursing home where it was possible to give the syrup-containing formulas from birth until 26 to 72 days of age, with an average period of observation of 44 days. In order to control the tendency to mild laxation in the first week of life, only one-half tablespoon of syrup was added to the milk and water during this period. After the first week 2 to 3 tablespoons of apple syrup were added to the total twenty-four-hour intake of each infant. Their average weight gain per week was 6.5 ounces. Of the entire series of newborn infants, two began to have loose stools at 8 and 10 days of age, respectively. After forty-eight hours, the syrup was replaced with another

carbohydrate and the symptoms subsided. There were no other instances of vomiting, regurgitating, diarrhea, or colic, which could be attributed to the syrup. The daily stools ranged from three to seven, the usual number being three or four. The color varied from dark yellow to brown, and the consistency was usually semisolid and unformed, with no mucus. No constipation was encountered. Serial hemoglobin tests of twenty-two newborn infants followed for the first 2 months of life showed the usual neonatal drop. The mean values were 21.8 Gm. per 100 ml. at one week, 16.2 Gm. at 4 weeks, and 14.2 Gm. at 9 weeks of age. These data are in conformity with the blood changes which have been observed in normal infants by Washburn[2] and others, during the neonatal period.

A small experiment was carried out to see how much apple syrup could be taken by newborn infants before marked laxation would occur. Using a group of eight infants aged one to 8 weeks, the content of syrup in the evaporated milk formula being fed was increased progressively every two days. With 4 tablespoons of syrup per 20 ounces of formula, no significant laxation occurred. When the proportion was raised to 5 tablespoons per 30 ounces, five infants exhibited frequent loose stools, which became normal when the syrup was reduced to 4 tablespoons again. The other three infants exhibited looseness and frequency of stools when given 6 tablespoons per 30 ounces, and this subsided after the amount was dropped to 5 tablespoons. These amounts are much higher than customarily given in infant feeding.

Two twin premature infants of birth weights of 3 pounds, 11 ounces, and 3 pounds, 12 ounces, were placed on an evaporated milk-apple syrup mixture on the second day of life, along with the usual vitamin supplements. The infants experienced no digestive difficulties and gained weight well. When discharged at the age of 5½ weeks, they weighed 5 pounds, 11 ounces, and 5 pounds, 15 ounces, respectively. Their hemoglobin levels at birth were 16.8 and 26.8 Gm.; at 5½ weeks, 17.2 and 17.6 Gm.

Sick Infants.—Milk formulas made with apple syrup have been fed to about fifty hospitalized sick infants. There were no transient disturbances when infants, whose feeding mixture had contained other carbohydrates prior to observation, were suddenly changed to similar ones made with apple syrup. These feedings appeared to be well-digested and absorbed, with no vomiting, colic, flatulence, or other symptoms of gastrointestinal irritation. One infant with severe eczema developed loose stools, which persisted after the apple syrup had been discontinued.

Although persistent infection of diverse types was present in most of these patients, the hemoglobin levels almost always maintained themselves without further drop once the apple syrup was given. When convalescence began, a rise in the hemoglobin was regularly seen. The rate of increment averaged approximately 0.5 Gm. per week.

Anemic Infants and Children.—Apple syrup was given in quantities of from 2 to 4 ounces daily to ten infants and children with nutritional anemia. Of these, two were in the hospital where they could be observed for some time, and the remainder were brought back to the Outpatient Department for regular follow-ups. No other iron-containing food or medication was given. The blood

response was uniformly in the direction of prompt regeneration. It was noted that some of these children could take amounts of the apple syrup up to 4 ounces daily without any gastrointestinal symptoms, whereas others would exhibit diarrheal stools when taking more than 3, or in some cases, 2 ounces daily.

This is a typical case history:

A 10-month-old girl baby had received no food except cow's milk with Dextri-Maltose since birth. When first seen she was well nourished but pale and had no sign of infection. Blood studies showed 5 Gm. of hemoglobin, 2.36 million red cells, and a reticulocyte count of 0.1 per cent. No medication or additional foods were given, but apple syrup was added to the milk in amounts of 6 tablespoons (3 ounces) per quart of milk. On her second visit seven days later, the reticulocyte count was 5.9 per cent, the hemoglobin was 7 Gm. per 100 ml., and the red cell count was 4.0 million per 100 ml. The apple syrup was continued. At the third visit seven days later, the reticulocyte count was 3.6 per cent, hemoglobin 9.6 Gm., and the red cell count 4.65 million. The child was now hungry, less pale, and wanting to eat solid foods. The apple syrup was discontinued and iron-containing foods given. At a follow-up visit five weeks later, the hemoglobin was 12 Gm.

Celiac Disease.—Apple syrup was given by spoon to eight children of preschool age, ill with celiac disease or other chronic intestinal disorders. From 3 to 6 tablespoons were taken daily for a period of two to six weeks. The syrup was liked by the children, and seemed to be well tolerated and absorbed. It produced no signs or symptoms of gastrointestinal distress or increase in number or bulk of the stools.

CONCLUSION

On the basis of clinical experience, a partly neutralized apple syrup standardized with added pectin has proved to be a satisfactory carbohydrate modifier for artificial infant feeding. The syrup does not produce gastrointestinal disturbances and is well tolerated. It mixes well, even with cold milk. It has a tendency to counteract constipation, and may have a laxative action if fed in excess. It should therefore be given in reduced dosage during the first week of life and in periods when the infant has a tendency toward loose stools. Presumably because of its nutritionally available iron, blood formation in children with anemia seems to be stimulated when the syrup is given.

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CONGENITAL ARTERIOVENOUS FISTULA OF THE CERVICAL VERTEBRAL VESSELS WITH HEART FAILURE IN AN INFANT

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ARTERIOVENOUS fistula as a cause of heart failure in infancy is a rare but interesting medical and surgical problem. Holman,[1] Callander,[2] and others have described fistulas of congenital or traumatic origin involving the carotid and jugular vessels, the subclavian, the tibial, the brachial, and intracranial vessels, but to our knowledge there is no instance on record of a developmental communicating vascular defect involving the cervical portion of a vertebral artery.

All arteriovenous fistulas do not eventuate in cardiac failure. According to Doane and Kravitz,[3] spontaneous closure may occur or, in some cases, the lesion may remain relatively symptomless throughout the normal span of life. Traumatic fistulas of the vertebral vessels have always been attended by greater risk to life than those of other locations, and the mortality rate in this group has previously averaged above 50 per cent.[4] This report deals with the record of a patient with congenital arteriovenous fistula of the cervical portion of the vertebral vessels which, under moderate stress, had caused cardiac decompensation and was successfully treated by surgical excision. The more important attendant circulatory phenomena are briefly discussed.

CASE REPORT

J. L. H., a 6-month-old white male infant, was admitted to Children's Hospital Dec. 11, 1948, with an acute illness provisionally diagnosed by his referring physician as meningitis. He had been born at term following an uneventful labor from a vertex presentation; there was no recognizable trauma to the neck region then or later. His immediate postnatal condition was excellent and remained so until the onset of the illness for which he was hospitalized. Growth and development had proceeded according to expectation.

At the age of 6 months he became ill with a cough and fever and was treated with penicillin and sulfadiazine without favorable response. Ten days later, December 11, signs of meningeal irritation suddenly appeared and an unsuccessful attempt had been made to obtain spinal fluid. One intramuscular injection of an unknown quantity of streptomycin was given and he was transferred to Children's Hospital.

Physical examination at the time of admittance revealed a well-nourished, moderately dehydrated infant who coughed frequently in a manner suggestive of bronchopneumonia. The rectal temperature was 105.8° F., the pulse rate 130 per minute, and the respiratory rate 44 per minute. The anterior fontanel was flat and pulsating, and there were no convincing signs of nuchal rigidity. The throat was slightly inflamed, and fine, moist râles were widespread in both lung bases. Examination of the heart was not considered to reveal abnormal

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findings at this time and all peripheral pulsations were present in normal intensity. There was slight edema of the scrotum and a small hydrocele of the left spermatic cord was found. No other abnormalities were noted. The weight was 17 pounds, 1 ounce.

The laboratory findings disclosed a red blood-cell count and hemoglobin value within physiologic limits, and a white blood-cell count of 15,800 per cubic millimeter with 37 granulocytes, 62 lymphocytes, and 1 monocyte identified in the differential count of 100 leucocytes. Culture of the pharyngeal secretions on blood agar grew only normal flora. Except for 200 mg. of albumin per 100 ml. of urine the urinalysis was not remarkable. The spinal fluid was normal, and the tuberculin skin test (1:1,000 O.T.) and the Kline serologic test were negative. Aerobic and anaerobic blood cultures were also negative. The serum total protein was 5.3 Gm. per 100 ml. X-ray studies of the chest disclosed a hilar inflammatory process on the right consistent with a diagnosis of hilar pneumonia, and a slight enlargement of the left ventricle.

Oxygen therapy was instituted without delay and antipyretic measures undertaken to reduce the infant's temperature. A course of intramuscular penicillin, 40,000 units every three hours, was initiated and intravenous glucose solution was started at a rate of 25 drops per minute and then slowed so that 2,500 ml. containing 2 Gm. of salt were infused during the first sixty hours. Oral feedings and fluids were also allowed. On the third hospital day the temperature became normal and the infant appeared to be somewhat improved although many fine râles remained throughout the lung fields and the cough was becoming more troublesome. He was, however, less active and a pitting edema of the lower extremities, the scrotum, and hands was now evident. The heart rate was 152 per minute and the liver had enlarged to extend 4 cm. below the right costal margin at the midclavicular line. For the first time a loud, continuous bruit with a systolic accentuation and a palpable thrill were discovered in the left posterior triangle of the neck. The bruit radiated to the crown of the head, to the base of the neck, and to the left elbow. There were no detectable temperature, color, or gross structural differences between the left and right sides of the head, and even in the area of most intense thrill there was no pulsatile mass. The infant was noted to prefer keeping his head turned toward the right. Fundiscopic examination was normal and roentgenograms of the skull and cervical spine failed to reveal any areas of erosion or abnormal calcification. By digital compression at the point of maximum bruit it was possible to produce an immediate fall of 25 beats per minute in the heart rate and a rise in blood pressure in the right arm from 88/26 to 106/54 (Branham's bradycardia reaction). A diagnosis of arteriovenous fistula of one of the major vessels in the left cervical region with associated heart failure was made. The infant was digitalized rapidly and given a mercurial diuretic and surgical repair of the fistula was planned.

At this point the cough became worse, assuming for the first time a paroxysmal pattern typical of pertussis. The white blood-cell count was now 10,000 per cubic millimeter with 78 per cent lymphocytes. A clinical diagnosis of pertussis was considered. Streptomycin, 50 mg. aerosolized every four hours, and sulfadiazine, 1 grain per pound per twenty-four hours, were administered and the third Bordet-Gengou plate inoculation was positive for *Hemophilus pertussis*. Human antipertussis serum was added to the therapy and gradual improvement in the paroxysms resulted during the second week of treatment. X-ray films of the chest now revealed definite left ventricular enlargement (believed to be due to dilatation) and pulmonary congestion, while repeated electrocardiograms showed prominent right axis deviation with an index of minus 130. Maintenance at more than twice the calculated dose of digitoxin finally brought the heart rate to 124 per minute but there were persistent râles

in the chest, mild dyspnea, and enlargement of the liver, all accentuated when the infant was removed from oxygen. The coincidence of pertussis caused considerable confusion in clinical assessment during this stage, but with no further improvement after two more weeks of treatment it was felt inadvisable to withhold surgery longer.

Accordingly, on Jan. 11, 1949, under general ether anesthesia a three-inch transverse incision was made in the left neck over the transverse process of the third cervical vertebra. The internal and external carotid and the transverse cervical arteries of that side were dissected out and inspected. The fistula with its vascular feeders was found overlying the transverse process of the second cervical vertebra and completely surrounded by the normally dense paravertebral connective tissues. The thrill could be obliterated by occluding the large vertebral arterial branch from below, or the vertebral artery and vein from above, but the aneurysm continued to pulsate until the other vessels were also occluded. Painstaking dissection permitted exposure of the fistula and its tributaries, which were carefully ligated, divided, and removed. The vertebral artery and vein were the prime vessels involved, and the fistula measured 8 mm. in diameter. (Fig. 1.)

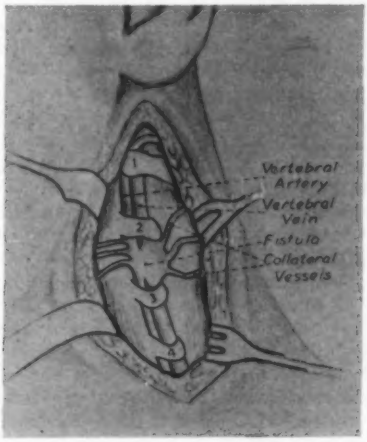

Fig. 1.—Artist's drawing depicting the fistula and its communications.

Microscopic description of the surgical specimen by Dr. H. D. Palmer, pathologist, was as follows: "The section is through the wall of a vessel. Since there is little or no musculature it is impossible to identify it as artery or vein. The intima is edematous, acellular, and thrown into folds. Many of the crevices between folds are lined by fibrin which is organizing. There is no cellular inflammatory reaction. The wall is predominantly collagenous fibrous tissue laid down in regular parallel bundles in the circular plane of the vessel." Two small calcified bodies were found free in the cavity of the gross specimen, the largest of which measured 3 mm. in diameter.

The pulse rate on the third postoperative day was 96 per minute and thereafter remained below 100. The bruit and thrill were absent. Respiratory symptoms disappeared on the second postoperative day and the lung fields rapidly became free of râles. Digitalis was discontinued and on the seventh day following surgery the patient was discharged in good health, weighing 17 pounds, 3 ounces. An x-ray film made that day revealed a notable decrease in the trans-

verse diameter of the heart and marked clearing of the pulmonary congestion. (Figs. 2 and 3.) Nine months later the infant continued in good health with no recurrence of the bruit.

DISCUSSION

Pathology and Physiology.—At gross examination there is little to distinguish a congenital arteriovenous fistula from a traumatic one except the absence of extensive scarring and the presence of numerous stellate vessels associated with the congenital lesion. Microscopic studies often decide the issue since the congenital fistula is characterized by minimal scarring, a lack of inflammatory reaction unless mycotic infection has occurred, and imperfect demarcation of artery from vein.

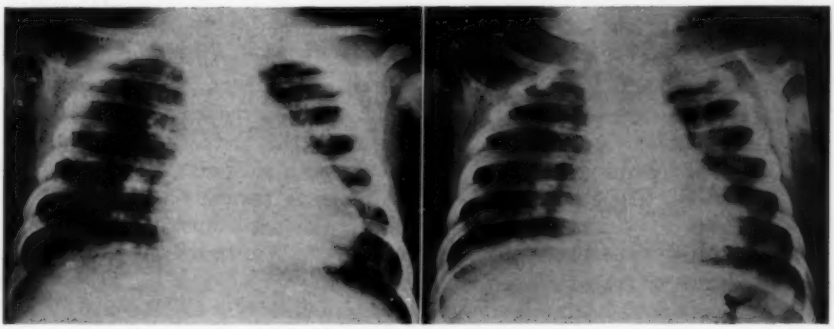

Fig. 2. Fig. 3.

Fig. 2.—Roentgenogram demonstrating the heart size prior to surgery.
Fig. 3.—Roentgenogram showing change in size and shape of the heart one week after excision of the fistula.

Any sizeable arteriovenous communication results in significant circulatory alterations; these have been extensively investigated and described.[5, 6, 7] At the time the fistula occurs there is a massive escape of blood under arterial pressure into the capacious venous system, depleting the arterial side and engorging the venous circulation. The immediate effect on the heart is similar to that of a sudden, severe, hemorrhage with a drop in blood pressure, particularly diastolic pressure, and a compensatory rise in pulse rate. The heart decreases in over-all dimensions and a state bordering on shock may follow. Blood volume determinations demonstrate that after from twenty-four to forty-eight hours the circulating volume may increase as much as 25 per cent in direct proportion to the volume shunted through the fistula, and that the increase is due to the addition of both cellular and fluid elements. The congenital fistula, of course, has no such acute onset, but similar alterations of vascular physiology occur more gradually, commencing at the time of the faulty development of the fetal vascular system. With expansion in blood volume the heart gradually enlarges and increases its stroke volume in an attempt to restore the blood pressure and pulse rates toward normal. Engorgement of the venous circuit dilates the large veins, the right auricle, right ventricle, and the pulmonary conus and arteries, producing changes of sufficient magnitude that they are usually demonstrable

clinically and radiographically. Left ventricular enlargement is mainly a result of dilatation with a minimum of hypertrophy, since the increase in minute volume is balanced against a decreased peripheral resistance and the increase in cardiac work remains minor. Small fistulas occasionally close spontaneously by thrombus formation[3] but usually there is gradual dilatation and increasing shunt of blood. Concurrently the vessels leading to the fistula, including the collateral vessels, tend to enlarge and carry an increasing percentage of the cardiac output through the short circuit and back to the heart.

Closure of the fistula initiates a physiologic readjustment that is in essence the reverse of the one just described. A comparatively large volume of blood is suddenly trapped in the arterial side of the circulation and the venous circuit becomes depleted, since the entire cardiac output must now circulate through the resistance of the peripheral capillary beds. There is immediate reduction in the size of the right auricle and the pulmonary conus, distention of the left ventricle, and marked distention of the aorta.[7] The distention of the left ventricle may provoke sudden left-heart failure in the immediate postoperative period, best treated by venotomy. Twenty-four to thirty-six hours later, providing the heart remains compensated, the circulating blood volume adjustment will have occurred. The heart then begins a return to normal size except for the small amount of hypertrophy that may have developed during the life of the fistula, and the blood pressure and pulse rate progress rapidly toward normal values.

Any variations in the circulatory dynamic effects of a fistula are the direct result of variations in the size, location, and duration of the communication.[7] The closer the fistula is to the heart, the greater is the hydrostatic pressure at its arterial end, and since the peripheral resistance in the artery distal to the defect is greater than that in the communicating vein, more blood passes through the fistula than were the defect more distal. With the passage of time circulation to the fistula by direct and collateral routes tends to increase and the volume of blood shunted into the vein progressively increases.

The disturbance of blood supply to tissues beyond the fistula is due in part to the small volume of blood reaching those tissues, but also to the fact that some venous blood may become admixed with the arterial blood by retrograde flow during diastole. The blood in the artery distal to the fistula, then, is likely to be in a partially reduced state, while that in the vein proximal to the fistula always carries a high oxygen saturation. It is also true that the increased hydrostatic pressure in the regional veins interferes with proper drainage of blood from the peripheral segments of those veins. Poor oxygenation and increased venous pressure account for the frequent occurrence of edema, cyanosis, and clamminess of the tissues distal to an arteriovenous shunt, and the rapid circulation of large volumes of blood through the proximal segments of the artery and vein account for the warmth and tendency to an increased rate of growth of those tissues in close proximity to the fistula.

Diagnosis.—The diagnosis of an arteriovenous fistula is not difficult but its exact localization may be perplexing, particularly if it occurs in the neck region.[4] Characteristically one finds over the area a loud, continuous bruit with a systolic

accentuation and a palpable thrill. Simple aneurysm of an artery is ruled out by Branham's bradycardia reaction. This test does not necessarily localize the fistula with precision, for pressure occluding the vein proximal to the fistula may produce the same result. Venous occlusion is the most likely explanation for demonstration of a positive Branham's reaction in our case and in those reported by others[4] wherein the fistula lies in the vertebral vessels at a point inaccessible to digital compression. Surface temperature is often increased proximal to the communication and decreased distally. Bones near a long-standing fistula are often increased in length and breadth and may have extensive engorgement of the marrow veins. Blood drawn from a regional vein may have a higher oxygen tension than blood drawn from a comparable opposite vein. Distal parts may become edematous from engorgement, and trophic changes to the extent of actual gangrene may develop. The heart and major vessels undergo the alterations described above. Intracranial fistulas produce an annoying bruit audible to the patient and usually to the examiner who places his stethoscope on the cranium. Those between the internal carotid artery and cavernous sinus result in ipsilateral engorgement of the retinal vessels and exophthalmos. Blood volume is abnormally high, and the increase is proportional to the volume of the shunt.

Accurate localization of the fistula is of prime importance to the surgeon. When there is a question concerning the exact point at which the fistula will be found, demonstration of the communication with a radiopaque dye is advisable. A simple, direct method is to insert a large trocar into the suspected artery proximal to the fistula and make angiograms. When the fistula is near the heart and the proximal portion of the suspected artery is not easily accessible, angiocardiography carried out in the usual manner has been successful in demonstrating the shunt.[8] Venography is applicable in fistulas near the roots of the extremities when the appropriate artery cannot be approached for injection due to anatomic difficulties.[9] In this procedure rapid injection of the dye into the proper wrist or ankle vein produces a radiopaque column terminating abruptly in the x-ray film at the level of the fistula.

Treatment.—Complete surgical excision is the only acceptable treatment for an arteriovenous fistula. All vessels entering or leaving the fistula are first ligated and excision of the fistula is then accomplished. Ligation of the artery alone should be avoided since the collateral circulation formerly supplying the tissues distal to the ligation would then drain directly into the vein via the fistula and little or none would overcome the peripheral resistance and supply the distal structures. Proximal ligation of the artery and vein may prevent gangrene, but as long as the fistulous tract remains patent the collateral arteries will continue to drain through it into the collateral veins.

A congenital arteriovenous fistula is probably best excised as soon after its discovery as circumstances warrant. On the other hand, a somewhat different problem exists with the management of traumatic fistulas. According to Doane and Kravitz[3] it is advisable to allow from three to six months for the establish-

ment of adequate collateral circulation to the extremity, absorption of the hematoma, and subsidence of infection incident to the injury before attempting its surgical excision.

One should not overlook the possibility of bacterial endarteritis becoming established on the immediate distal side of the fistula. It is most often secondary to subacute bacterial endocarditis involving the aortic valve.[10] Treatment is then that of subacute bacterial endocarditis plus surgery.

SUMMARY

A case of arteriovenous fistula involving the cervical portion of the left vertebral vessels and producing or contributing to acute reversible heart failure in a 6-month-old male infant is reported. No comparable case has been found in the available medical literature. Ligation and excision of the fistula resulted in prompt return to a normal status of the decompensated heart. A short review of the interesting basic facts relating to the general subject of arteriovenous fistula is presented.

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PERIARTERITIS NODOSA ASSOCIATED WITH RATBITE FEVER DUE TO STREPTOBACILLUS MONILIFORMIS (ERYTHEMA ARTHRITICUM EPIDEMICUM)

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THE first pathologic description of periarteritis nodosa was made in 1852 by Rokitansky,[1] but it was not until 1866 that Kussmaul and Maier[2] named the disease and correlated the clinical and pathologic observations. Since that time, the majority of cases have been reported in the age groups occurring between the third and fourth decades. Brennemann[3] states that 30 cases have been reported in children; 2 occurring during the first year, 8 from the second through the ninth year and 22 between the tenth and fifteenth year. In 1941 Keith and Baggenstoss[4] summarized the clinical aspect of 44 cases of periarteritis nodosa occurring in children; they collected 42 cases from the literature (including those by Rothstein and Welt[5] in 1933), and added 2 cases of their own.

With the comparative paucity of reports of periarteritis nodosa in children, it is indeed rare that such a case should come to our attention, combined with the even more rare condition of ratbite fever caused by *Streptobacillus moniliformis*. A search of the literature does not reveal any similar combination of conditions.

CASE REPORT

J. H., a 9-year-old white male child, was in good health until one week before entry, when he developed a mild upper-respiratory infection with cough. This subsided, but a red, macular rash appeared on the legs and then on the forearms. The individual lesions were situated rather deeply in the dermis and varied in size up to one cm.; they eventually became hemorrhagic, then disappeared, leaving a purplish-brown discoloration which gradually faded. This was accompanied by edema of the extremities, which also involved the face on the day of entry. There was a complaint of aching bones and joints of several days' duration, accompanied by a limp the previous day. At that time he had complained of leg pain and had fallen while carrying dishes. There had been no swelling or redness of the joints, nor was there any more complaint of articular pain during the subsequent course of his illness. He had vomited intermittently for the previous two days.

The previous history was noncontributory except that he had received a bite approximately one week previously, while attempting to catch a white rat that had escaped from a playmate. The wound was healed, and the scar was found with difficulty on the right index finger at the nail base. No change occurred at this site during the subsequent illness. The rat had promptly been shot and burned by the boy's father. The history further revealed that there had been no prior administration of sulfonamides, sera, antitoxins, or drugs that could have been of significance in the development of the subsequent illness.

The boy was pale and listless but appeared to be in no distress. Physical examination revealed palpable, discrete, anterior cervical lymph nodes, but nothing else of significance except for the fading rash and nonpitting edema already described. The blood pressure was 150/90.

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A twenty-four-hour urine specimen revealed 4-plus albumin, 10 to 12 pus cells, 0 to 2 erythrocytes, 10 to 15 granular casts, and 0 to 2 cellular casts per high power field. The red blood count was 3.91 million, hemoglobin 11 Gm., white blood count 11,000. Of 100 cells counted 77 were neutrophiles, 17 lymphocytes, 6 monocytes. The sedimentation rate was 42 mm. per hour and the prothrombin time normal. The blood urea was 115 mg., serum cholesterol 162 mg., plasma protein 6.4 Gm., albumin 3.65 Gm., globulin 2.75 Gm. per 100 ml. of blood. The blood Wassermann was negative.

Urinary output was very scanty during the early days of hospitalization but gradually increased to 1,000 ml. daily. After the second day the urine became frankly bloody and the casts disappeared. The presence of albumin and blood cells did not change. Anemia became marked in spite of four transfusions. The white blood cells varied from 19,000 to 24,000 and eosinophiles appeared in the peripheral blood, at times being as high as 15 for 100 cells counted. The plasma protein remained within normal range but there was a reversal of the albumin-globulin ratio. The sedimentation rate rose to 76 mm. per hour, and later fell to 42. The blood urea reached 202 mg. per 100 ml. of blood. A blood sample sent to the Public Health Institute for agglutination test to rule out ratbite fever was reported unsuitable for testing. A second sample taken at the time of autopsy was reported as giving a positive agglutination test for *S. moniliformis* in titer as high as 1:1,280.

The patient became progressively worse. Abdominal pain was a constant complaint, and he was almost never free of nausea and vomiting. Little food was taken voluntarily and tube feedings of a high protein, salt-poor diet were given, but retained poorly. The vomitus occasionally contained blood. There was considerable bloody crusting of the nares which the patient constantly pulled loose, causing bothersome oozing. Roentgenograms of the sinuses showed clouding of the left antrum, and roentgenograms of the chest showed the heart and aorta to be within normal limits and the lung fields to be clear. The patient's weight which was 76 pounds on entry gradually dropped to 65 pounds. A soft systolic murmur, thought to be hemic, developed.

On the eighth hospital day the urinary output fell to 675 ml., the blood pressure, which had fallen, again rose to 120/90, and edema reappeared in the feet, hands, and face accompanied by symptoms of cerebral edema. There was a divergent squint of the left eye with inability to converge, and tremor of the extremities was marked. He was drowsy and unresponsive and lay in partial opisthotonus. The optic fundi showed no papilledema, and a spinal fluid examination was essentially normal. The cerebral edema gradually disappeared over a three- to four-day period. On the tenth hospital day a coarse maculopapular erythematous rash appeared on the back and lower extremities, which gradually spread over the whole body. The rash remained with minor variations throughout the rest of hospitalization. With the third transfusion, petechiae appeared on the extremities where the tourniquet was applied. The rectal temperature showed daily variations up to 102° F. but followed no definite pattern. The blood pressure dropped as low as 110/60 but the diastolic pressure was frequently recorded as high as 90 with a systolic varying from 120 to 138.

Dosage of 300,000 units of procaine penicillin was given daily until the sixth hospital day, then discontinued. On the thirteenth hospital day aqueous penicillin was started in divided doses and this was changed to procaine penicillin on the eighteenth hospital day. All penicillin was stopped on the twenty-ninth day. Other medications included rutin, vitamin B complex, iron, nose drops, and ascorbic acid.

The patient's general condition gradually deteriorated and symptoms of uremia developed. He died on the thirty-eighth hospital day.

The autopsy, which was performed three hours after death, revealed a well-nourished male child who was large for his stated age of 9 years. A summary of the pertinent gross observations follows. A fine, slightly raised, slight brown to purplish-brown cutaneous rash was limited to the upper and lower extremities. The rash started just above the elbows and knees and was particularly prominent on the flexure surfaces and the dorsum of the hands and feet. There were small hemorrhages in the pericardium, thymus, visceral pleura, and right testis. The mesenteric lymph nodes were slightly enlarged but there were no visible nodules along the course of the visceral arteries. The heart was considerably enlarged, weighing 220 grams as against an expected weight of 115 grams. Over the apex there were a few pale gray nodules along the course of the small branches of the descending branch of the left coronary artery. There were several similar nodules along the terminal portion of the right coronary artery on the posterior surface of the heart.

The liver weighed 1,010 grams, which is one-third more than its expected weight of 756 grams, but otherwise it appeared normal. On gross inspection the gastrointestinal tract showed only hyperemia of the mucosa. Both kidneys were approximately twice normal size. Their external surfaces were pale yellowish-brown, diffusely and finely mottled with bright red. Sections revealed bulging, pale yellow cortices poorly demarcated from the darker pyramids. There were numerous bright red and pale gray, circular foci less than 1 mm. in diameter in the cortices. The pelves and calyces were filled with clotted blood and their lining mucosae were edematous and dark red. The mucosa of the urinary bladder was thickened and section revealed a submucosal layer of blood several millimeters in thickness. The brain was not examined; this was unfortunate, considering the clinical aspects of the case suggestive of central nervous system involvement.

Microscopic examination showed lesions typical of the acute and healing stages of periarteritis nodosa in all organs except the skin, lungs, and spleen. The lesions of the terminal branches of the coronary arteries showed the most advanced stages of the disease with evidence of healing and scarring. The lumens of the arteries were greatly narrowed by medial proliferation. The perivascular infiltrate was scanty and consisted of lymphocytes and plasmacytes. Careful search of many sections of the lungs showed no lesions which could be interpreted as representative of an allergic condition or asthma.

There was a patchy involvement of the small portal arteries of the liver by a typical fibrinoid necrosis of the media and a polymorphonuclear exudate in the adventitia and media. Many submucosal arterioles and small arteries of all sections of the gastrointestinal tract except the esophagus showed characteristic lesions with little evidence of healing. One or more eosinophils were seen in all acute lesions.

Many sections of the kidney showed conspicuous vascular changes chiefly in the small parenchymal arteries. Some could be identified only by a ring of pink-staining material. Their lumens were filled with fibroblasts and polymorphonuclear cells. One small artery showed an arciform bulging of the fibrinoid ring and probably represented an aneurysm. Some arteries showed a healing stage. Other renal changes included a focal glomerulitis and blood and cellular casts in the tubules.

The anatomic diagnoses were: periarteritis nodosa, involving thymus, heart, liver, gallbladder, stomach, jejunum, ileum, appendix, colon, pancreas, kidneys, urinary bladder, right testis, and adrenals; anemia; focal infarcts of kidneys and adrenals; small hemorrhages in thymus, visceral pleura, pericardium, periadrenal fat on the right, and right testis. A positive serologic test for *S. moniliformis* in dilution 1:1,280 warrants the inclusion of the diagnosis of ratbite fever due to *S. moniliformis*.

COMMENTS

The following clinical diagnoses were suggested early in the course of the patient's illness: ratbite fever, rheumatic fever, periarteritis nodosa, and acute glomerulonephritis. Lack of clinical improvement to administration of penicillin was accepted at the time as presumptive evidence that the boy probably did not have ratbite fever caused by the *S. moniliformis*, or, if present, it was overshadowed by another condition of a graver nature. Rheumatic fever was not seriously considered as a possibility after the first few days, as migatory arthritis and the usual cardiac manifestations of that condition were lacking. The clinical course characterized chiefly by abnormal urinary sediment, albuminuria, elevated blood pressure, the presence of symptoms which could be attributed to cerebral edema and uremia, and the absence of subcutaneous nodules made the diagnosis of acute glomerulonephritis appear more tenable than the diagnosis of periarteritis nodosa.

The autopsy observations were those of a typical periarteritis nodosa and were not those which would be expected in rat bite fever. There are no specific or pathognomonic lesions by which ratbite fever can be diagnosed anatomically, either grossly or microscopically. Anderson[6] and others[7, 8, 9, 10] state that the lesions of ratbite fever are similar to those of any acute infection while vascular lesions of the type seen in periarteritis nodosa are not reported or seen in infectious diseases of known etiology.

The terminal branches of the coronary artery showed the only lesions which grossly were suggestive of periarteritis nodosa. Grossly, the kidneys were those of an acute stage of glomerulonephritis, but microscopically the renal lesions were primarily vascular, and the glomerular and interstitial changes are considered secondary to the presence of these changes in the glomerular arterioles and capillaries.

The rash which was noted by one of us (E. L. S.) at autopsy probably had a different etiology from that noted during the clinical course. It was probably secondary to an increased capillary fragility and not to the periarteritis nodosa per se, as typical lesions of that disease were not found on microscopic examination of numerous sections of the skin. It was later learned that an intern had applied a tourniquet to the opposite arm and both legs when petechiae were observed during the administration of intravenous blood. As the petechiae faded, a tiny, pale brown crust formed at the site. In retrospect it is impossible to state whether the original rash seen on the ankles was the rash of ratbite fever or periarteritis nodosa. Similarly, it is impossible to state whether the rash which reappeared on the third and tenth hospital days was caused by one or the other of the preceding conditions or whether it may have represented the development of a sensitivity to some drug. This rash consisted of erythematous macules and papules and occurred first on the face and thighs and later involved the entire body. The appearance of the rash was unrelated in time to the administration of the penicillin, which would seem to be the most likely offender.

The history of a rat bite shortly before the onset of the acute illness and the positive agglutination test for *S. moniliformis* in high titer[11] can be accepted as evidence that the patient had or had previously had ratbite fever. Failure

to grow the organism from the blood at autopsy in no way invalidates this conclusion, as the patient had received large amounts of penicillin throughout the hospital course and this should have eliminated the *S. moniliformis* from the blood stream.

DISCUSSION

The cause of periarteritis nodosa has been a much debated point, and has never been specifically determined. The streptococcus organisms have been commonly suspected, but blood stream invasion has not been proved. However, it runs a septic course with remitting fever and leucocytosis. Spiro[12] postulated that it was a postinfectional mesarteritis resulting from various causes. Harris and Friedrichs[13] claimed to have transmitted the disease to rabbits by a filtrate from a human lesion, and to have produced even more striking lesions in a second rabbit inoculated from the first. From this they concluded that periarteritis nodosa was a specific infectious disease of viral origin. Their results have not been confirmed by other investigators. Friedberg and Gross[14] believe that rheumatic fever is a common cause, since the two lesions commonly coexist and in their opinion resemble each other. In 1925 Gruber[15] was first to suggest that it might be an allergic manifestation. Cohen, Kline, and Young[16] contend that the disease is a severe manifestation of clinical allergy. They call attention to the histologic similarity between the lesions of periarteritis nodosa and those induced by injections of foreign proteins into the skin. Most of their patients showed eosinophilia.

Diagnosis is often very difficult before autopsy, but the clinical picture includes many of the following: (1) A septic, irregular, or remittent fever is present. (2) Tachycardia is the rule, and if out of proportion to the degree of fever it may indicate cardiac involvement. (3) Leucocytosis may range from 10,000 to 20,000 or higher. (4) Polymorphonuclear cells tend to predominate although eosinophilia is striking in some cases. (5) About one-half the patients have abdominal pain which may be severe enough to simulate an acute surgical abdomen. (6) Renal symptoms have already been mentioned and uremia is a common cause of death. (7) About one-half the patients show clinical signs of central nervous system involvement[5] such as hemiplegia, cerebellar ataxia, headache, vomiting, and vertigo. This wide variation in clinical symptoms depends upon the location of the pathologic process. Brennemann[3] states that the mortality is close to 95 per cent.

Leaving the discussion of periarteritis nodosa for the time being, let us discuss the coexisting condition of this case.

Ratbite fever may be caused by one of two organisms, but for purposes of this paper we will limit ourselves to the discussion of the *S. moniliformis*. This was first adequately described in 1914 by Schottmüller.[17] In 1926, an epidemic supposedly caused by a milk-borne organism occurred in Haverhill, Mass.[18] The organism isolated by Parker and Hudson[19] was named *Haverhillia multiformis* and later changed to *Streptobacillus moniliformis*.[20] This organism, which is saprophytic in animals, is pathogenic in humans. The disease in man is known as Haverhill fever when produced by the ingestion of the organism and

as ratbite fever when the organism is introduced by the bite of an animal. The wound heals within a few days; the disease onset usually begins abruptly after an incubation period of from one day to three weeks (usually five days). Diagnosis may be made by finding the organism in body fluids, or by an agglutination titer of 1:80[11] or more. Usually there is a history of a rat bite, although other animals[21, 22] or contaminated food or drink may be the source of transmission.

Data concerning symptoms and the course of the disease in our patient have been summarized in Table I. Here we have compared two dissimilar conditions which have certain points in common. This was done in an attempt to determine which of the two diseases was responsible for the symptoms found in our case.

TABLE I

	ERYTHEMA ARTHRITICUM EPIDEMICUM	PERIARTERITIS NODOSA
Cause	*Streptobacillus moniliformis*	Unknown
Incidence	More common in children	More common in adults
Onset	Sudden onset of chills and fever, headache, arthritis, vague muscular pain, general malaise	Onset variable, acute or insidious, may develop sudden abdominal pain, may have arthritis, polymyositis, neuritis, headaches, weakness
Signs and symptoms		
Fever	Usually intermittent, septic, rarely relapsing	Irregular
Pulse	Tachycardia	Tachycardia
Rash	Large or small macules or papules, erythematous, occasionally petechial	Variable, subcutaneous nodules not constant, macules or papules may be purpuric
Pain	70% have painful, swollen, red joints; commonly have headache, myositis, neuritis, abdominal cramps, nausea, vomiting	May have arthritis, commonly have headache, myositis and neuritis, abdominal cramps, nausea, vomiting
Clinical manifestations		
Red blood cells	Anemia, not common	Anemia, often profound
White blood cells	Leucocytosis 10,000-30,000	Leucocytosis 10,000-20,000 Frequent eosinophilia
Urinary findings	Albuminuria, hematuria, casts, edema, nitrogen retention, elevated blood pressure—variable. Symptoms of nephritis usually not severe or prolonged	Albuminuria, hematuria, casts, edema, nitrogen retention, blood pressure frequently elevated
Prognosis	Probably not over 10% mortality	90-95% mortality
Cause of death	Toxemia or uremia	Depends on systems involved. Uremia a frequent cause

Death from ratbite fever due to *S. moniliformis* is not common. Anderson[6] places the mortality rate at 10 per cent, which seems high after a study of compiled reports. Very likely there are a number of mild unrecognized and unreported cases. The prognosis is said to be grave when the infection is accompanied by anemia, nephritis, or continued fever.

The renal symptoms in this case were probably due originally to ratbite fever but continued unabated as the kidney became involved by the lesions of periarteritis nodosa. The point at which one disease subsided only to be replaced by the similar symptoms of the other is hard to evaluate. Perhaps the onset of the second rash on the tenth hospital day furnishes the clue. In the second week other symptoms became more marked, nausea and vomiting were more bother-

some, anemia became more severe, and the sedimentation rate rose. In this case prognosis was guarded from the first as the patient so quickly developed severe anemia and a nephritic syndrome. The further complication of periarteritis nodosa led to terminal uremia.

Whether the ratbite fever was concurrent with or antedated and perhaps initiated the periarteritis nodosa cannot be stated with certainty. Nor can we be certain that the two disease processes did not exist independently. We can only speculate upon the development and relationship of the two diseases in our case, but we believe that the ratbite fever probably was the initial illness with the periarteritis nodosa developing subsequently. A short review of the probable course will substantiate this. A previously healthy boy received a rat bite and four or five days later developed a macular rash on the legs and arms which became hemorrhagic and then faded. At the same time he complained of articular pain, vomited, and developed edema of the legs and face. These symptoms, which are typical of the onset of ratbite fever, came within the usual incubation period of one day to three weeks. If one accepts this sequence of events the question of the possible relationship between the two diseases arises. Was the periarteritis nodosa unrelated to the ratbite fever? Did the infection (ratbite fever or some drug used in its treatment) produce a change in the tissue proteins so that exposure to some subsequent allergen, in this case penicillin, resulted in the profound vascular phenomena of periarteritis nodosa? The latter assumption offers an attractive explanation for the occurrence of an unusual disease in a previously well child without an allergic or hypersensitive history. There is considerable experimental[23] and clinical evidence[24, 25, 26] that altered tissue reactivity may be a causative factor in the production of periarteritis nodosa. Also, there is experimental evidence to support Rich's[27, 28, 29] claim that plasma proteins may combine with certain substances or drugs to form antigens which in turn are capable of producing antibodies which react with the original antigen to produce serum sickness and histologic vascular changes indistinguishable from those of periarteritis nodosa. A number of drugs have been implicated as the probable cause of periarteritis nodosa, notably the sulfonamides,[24, 25] but others have been suspected: namely, iodine,[26] Diodrast, and Dilantin Sodium.[30] Many other drugs are known to have toxic effects. Some of the reactions, namely, fever, cutaneous rashes, eosinophilia, and angioneurotic edema, are thought to be manifestations of allergy. These allergic reactions have been ascribed not only to the above drugs but also to thiouracil,[31] penicillin, and streptomycin. Of all the drugs listed above only penicillin was used in this case. No definite time relationship could be established between the administration of penicillin and the appearance of the rash, but the intermittent administration of penicillin gave ample opportunity for the tissues to become sensitized. Uhr and Chess[32] reported a case of periarteritis nodosa in a patient which they thought was aggravated by the administration of penicillin subsequent to earlier penicillin therapy. Sullens[33] reported a case of a patient simulating serum sickness resulting from penicillin. Hopkins and Lawrence[34] have found that a few patients (0.8 per cent of a series) had been rendered so sensitive to penicillin, which was used in treatment of cutaneous lesions, that its subsequent internal use was

prevented. Chow and McKee[27] have shown that penicillin can combine with serum albumin to form a substance which acts as a hapten to combine with body proteins to form a sensitizing agent.

SUMMARY

The preceding case is the first to be reported of ratbite fever coexisting with periarteritis nodosa. The ratbite fever was proved by agglutination tests, and the periarteritis nodosa was verified by autopsy observations. The report is accompanied by a discussion of the literature and comments on the possible etiology of the periarteritis nodosa.

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THE USE OF PERTUSSIS AGGLUTINOGEN SKIN TEST DURING ACTIVE INFECTION WITH WHOOPING COUGH

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MILLER, Ryan and Havard[1] have recently reviewed the use of the pertussis agglutinogen skin test as an index to immunity to whooping cough. This test, as described by Felton and Flosdorf[2] and by Flosdorf, Felton, Bondi, and McGuinness,[3] employs as antigen a purified nontoxic protein fraction of *Hemophilus pertussis,* obtained first by sonic extraction and later by acid extraction. The acid-extracted material was reported to be more potent and does not contain any *H. pertussis* endotoxin. The antigen was called an agglutinogen because of its capacity to absorb agglutinins from immune serum, and it was standardized with this as a basis.

This agglutinogen has been used for skin testing by some[3, 4, 5, 6] before and after the use of prophylactic *H. pertussis* vaccine. There have been very few reports on the use of the skin test during and after the course of whooping cough. In this communication we shall report on the results of this skin test performed during the course of whooping cough at the Willard Parker Hospital.

METHOD AND MATERIAL

There were 292 children ill with whooping cough who were tested with the agglutinogen. None had received any prophylactic vaccine. Because of the difficulties in establishing a diagnosis of whooping cough in young children, only a small number were admitted and available for testing before the paroxysmal stage.

For the test 0.1 c.c. of agglutinogen was injected intradermally. The site was examined after twenty-four and after forty-eight hours. The criteria of Flosdorf and Felton[4] were followed in interpreting the reactions. An area of induration of one square centimeter or more was considered an immune reaction (10 mm. or more in diameter). A reaction of lesser size or no reaction at all was interpreted to indicate susceptibility. Erythema without induration was not considered significant.

The children in our series were tested during the courses of three different studies of the treatment of whooping cough. The first and second, during a study on the use of streptomycin,[7, 8] and the third during a study on the use of Polymyxin B.[9] Nasopharyngeal cultures for *H. pertussis* were done in all patients during the course of these studies. The first series included patients admitted from April 1 to Sept. 30, 1947 [a total of 123 children (L. W. W.)], the second, from Jan. 1 to July 1, 1948 [a total of 44 children (K. S. S.)], and the third from July 1 to Dec. 31, 1948 [a total of 125 children (S. R. K.)].

In groups 1 and 3 the skin tests were not repeated more than once and then only if the first test was negative. In Series 2 the tests were repeated frequently.

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RESULTS

The reactions obtained to the agglutinogen skin test are shown in Table I. Since Felton and Flosdorf[4] have shown that repeated injections of agglutinogen may lead to the production of antibodies, one cannot compare resultant skin tests of Group 2 with those of Groups 1 and 3. In Group 2 in which the skin tests were done more frequently, an average of 3.3 tests per patient, we found that 91 per cent of the skin tests were positive before discharge. Whereas in Groups 1 and 3 when an average of 1.3 and 1.7 tests per patient were made, the positive tests ranged from 61 per cent to 65 per cent. The results obtained with the test were inconsistent. Some children were found to have a positive reaction during the second week after the onset of illness and others did not show positive reactions until the sixth week.

TABLE I. RESULTS OF AGGLUTINOGEN SKIN TEST DURING WHOOPING COUGH*

GROUP NO.	NO. OF PATIENTS TESTED	NO. OF TESTS PER PATIENT	NO. OF PATIENTS POSITIVE	PERCENTAGE POSITIVE
1	123	1.3	75	61
2	44	3.3	40	91
3	125	1.7	81	65

*Note in Group 2 the influence of repetition of this skin test.

It is often stated that a skin test in children under 6 months of age is unsatisfactory and unreliable. When tested, in Group 3 about the same percentage of positive tests was obtained in the young group when compared with that of older children. An attempt was made to correlate the skin test with the severity of the illness but there was no correlation.

It was also noted that when skin tests were done on nurses, physicians, and other personnel on the whooping cough service, a negative test was usually obtained. In many of these adults a definite history of whooping cough during childhood was obtained.

DISCUSSION

The pertussis agglutinogen skin test to determine the immunity of whooping cough offers many difficulties. The test is often difficult to read since the resultant reaction is not always clear-cut. Induration of a certain size was given as a criteria for a positive reaction. Perhaps a better evaluation of the test could be gotten if the same individuals could read the skin reactions over long periods of time. A physician who has occasion to read only a few tests is frequently in doubt as to how to interpret the skin reaction. The induration is often not visible and is determined by palpation. In our experience the test should be read at the end of twenty-four hours. Occasionally, however, the reaction was not developed fully until the end of forty-eight hours.

Miller and associates[1] have shown that a higher serum agglutinin is obtained after a course of prophylactic vaccine with *H. pertussis* than that obtained after the actual illness. It has been shown by Miller and associates, and others that significant titers of agglutinins are obtained in the serum after about three weeks of illness. The agglutinogen skin test has been found to be positive following the use of vaccine in a very large percentage of children. A much

smaller percentage of positive reactions have been found soon after recovery from whooping cough. Miller and his associates[1] found only one positive skin agglutinogen skin reaction in 10 children during recovery from whooping cough. Felton and Flosdorf[2] found positive skin reactions in 90 of 113 children who had had positive histories of whooping cough from six months to ten years previously. In another series, Flosdorf and associates[3] obtained positive tests in 194 of 218 children.

In our experience, the reactions obtained during the course of whooping cough were not consistent. Positive tests were obtained early, others became positive late, and some remained negative throughout their hospital stay.

SUMMARY AND CONCLUSIONS

The pertussis agglutinogen skin test was made in 292 children ill with whooping cough. The resultant test showed positive before discharge in 156 of 248 children (62.9 per cent), if no more than two tests were made. When more than two tests were done, the percentage of positive tests was much higher.

In some children, the test was positive early in the disease.

Personnel on the whooping cough service who had a history of illness during childhood were found to have a negative skin test.

The reaction following the skin test was often difficult to interpret.

We do not believe that the agglutinogen skin test can be used as an accurate index of immunity following an infection with whooping cough.

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OSSIFICATION OF THE METACARPAL AND METATARSAL CENTERS AS A MEASURE OF MATURATION

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THIS report is concerned with the usefulness of the centers of ossification of certain metacarpal and metatarsal epiphyses as measures of maturation between one and 5 years of life. The bones most suitable for clinical purposes are the epiphyses of the first and second metacarpals and the second, third, and fourth metatarsals. The convention has been followed of numbering the bones from one to five, beginning with the thumb or great toe as one. The reason for choosing these bones is that they show the least variability in the ages at which they appear.

Todd[1] has pointed out that at all ages, primary centers (carpals and tarsals) show considerably more variation than secondary centers, with the exception of the capitate and hamate bones which ossify within the first three or four months of life. He concluded that the epiphyses of the metacarpals, metatarsals, and phalanges are the most useful ones for determining bone age under 6 years.

Calculations in the tables and figures are based on the data of Francis and Werle.[2] They studied a selected group of 307 boys and 315 girls in Cleveland, Ohio, and made a total of 1,728 observations at varying intervals over a period of five years. Their data were presented in tables showing the number and per cent of children having the various centers at certain age intervals from birth up to 5 years of age.

For the purpose of this presentation the findings of Francis and Werle were plotted graphically, curves were drawn to fit the point, and the curves were then smoothed. The calculations in the tables are based upon the smoothed curves.

Table I shows the percentage of girls and boys, respectively, with ossification of the centers under consideration at specified ages. The data for some of the bones are illustrated in Fig. 1. Table II gives the mean age of appearance and the standard deviation of the age for each of the centers under consideration. It is interesting to note that in a similar survey conducted by Elgenmark[3] on Swedish children, the age of appearance of these bony centers lags behind that of American children by one to seven months.

Table I permits a fairly accurate assessment of bone age between the ages of one and 5 years. For example, at one year of age about 50 per cent of girls show ossification of the center for the second metacarpal and only 8 per cent have an ossified center for the first metacarpal. In only 4 per cent of the cases is there a metatarsal center. At 2 years of age practically all girls have all their metacarpal centers and 60 per cent have the second metatarsal epiphyses.

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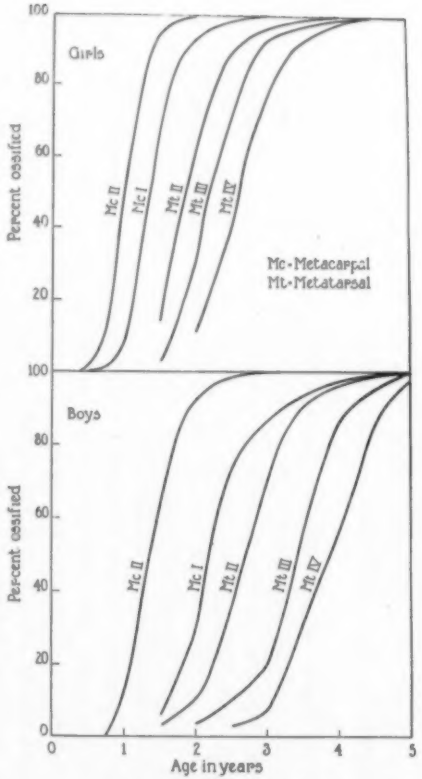

Fig. 1.

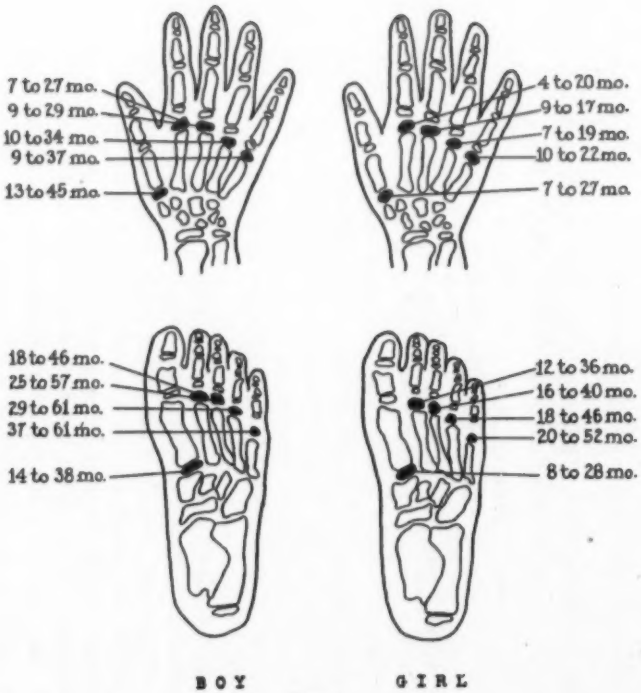

Fig. 2.

Fig. 1.—Percentage of children with ossified centers by ages from 6 months to 5 years. Graphic representation of data in Table I.

Fig. 2.—The age ranges for the appearance of the metacarpal and metatarsal centers. Age ranges include two standard deviations above and below the means (about 95 per cent of cases).

At 3 years of age only the center for the fourth metatarsal remains unossified in a significant percentage of cases and at 4½ years all of the bones under consideration are ossified in 100 per cent of girls.

The appearance of these centers in boys occurs from six to thirteen months later than in girls. The sex difference is shown most strikingly in the ossification of the center for the first metacarpal. The average age for the appearance of this center in girls is 17 months, twelve months earlier than in boys. Whereas practically all girls have an ossified first metacarpal at 2½ years, this does not take place until 3½ years of age in boys. A similar lag is apparent in all of the centers, ossification not being completed in 100 per cent of boys until 5 years of age, whereas in girls it is virtually complete one year earlier.

The age of appearance of each center, expressed in terms of the mean and standard deviation, appears in Table II. The calculations are based upon the assumption that the distribution curves for each bone are symmetrical, although

TABLE I. PERCENTAGE OF CHILDREN WITH OSSIFIED CENTERS BY AGES FROM 6 MONTHS TO 5 YEARS. THE MOST USEFUL BONES ARE IN HEAVY TYPE

AGE IN YEARS	6 MONTHS	9 MONTHS	1	1½	2	2½	3	3½	4	4½	5
Girls											
Metacarpal II	2	12	48	96	100						
Metacarpal III	2	9	43	95	99	100					
Metacarpal IV	1	5	32	88	99	100					
Metacarpal V	1	3	14	78	96	99	100				
Metacarpal I	1	1	8	65	94	99	100				
Metatarsal I		1	4	49	89	97	100				
Metatarsal II				14	60	90	97	98	100		
Metatarsal III				3	31	69	94	97	99	100	
Metatarsal IV					11	38	76	93	97	100	
Metatarsal V					4	24	44	72	89	92	95
Boys											
Metacarpal II		1	13	62	94	99	100				
Metacarpal III			6	38	86	97	98	100			
Metacarpal IV			4	26	72	93	96	100			
Metacarpal V			1	18	57	88	91	100			
Metacarpal I				6	29	74	80	98	95	98	100
Metatarsal I				2	31	75	87	98	100		
Metatarsal II				3	10	45	70	94	95	98	100
Metatarsal III					4	10	20	57	87	96	100
Metatarsal IV						3	7	32	56	86	98
Metatarsal V						3	4	13	41	78	94

TABLE II. AGE OF APPEARANCE OF CENTERS OF OSSIFICATION

BONE	MALE		FEMALE	
	MEAN AGE (MO.)	STANDARD DEVIATION (MO.)	MEAN AGE (MO.)	STANDARD DEVIATION (MO.)
Metacarpal II	17	5	12	4
Metacarpal III	19	5	13	2
Metacarpal IV	22	6	13	3
Metacarpal V	23	7	16	3
Metacarpal I	29	8	17	5
Metatarsal I	26	6	18	5
Metatarsal II	32	7	24	6
Metatarsal III	41	8	28	6
Metatarsal IV	45	8	32	7
Metatarsal V	49	6	36	8

in actual fact the curves are slightly skewed. Elgenmark[3] calculated the skewness of these curves and concluded that it is not statistically significant but is due to the small size of the population studied. Standard deviations were included in this presentation because they provide the most useful measures of variability. Fig. 2 shows the ages of appearance of the metacarpal and metatarsal centers.

SUMMARY

The ossification of certain metacarpal and metatarsal epiphyses is useful in assessing bone age between the ages of one and 5 years.

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SICKLE-CELL ANEMIA IN YOUNG INFANTS

Report of Two Cases

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ALTHOUGH sickle-cell anemia is a well-known clinical entity, there has been very little mentioned in the literature about cases being found in infants. Since Herrick[1] first described sickle-cell anemia as a definite disease in 1910, there has been a minimum of cases diagnosed in young infants. However, there have been a number of cases of latent sickling or sicklemia reported during infancy. In 1928, Anderson and Ware[2] reported a case of active sickle-cell anemia in a 7-month-old Negro infant. In 1939, Arena[3] reported a case of sickle-cell anemia in a 9-month-old Negro male infant with lobular pneumonia. A patient was described by Stewart[4] in whom the symptoms were present at the age of 10 months, but sickle-cell anemia was not diagnosed until the age of 16 months. Sydenstricker[5] has stated that he had no knowledge of any case of active sickle-cell anemia found in an infant as young as one of the patients presented in this paper. With the lack of information in the literature on sickle-cell anemia in young infants, it was felt that it would be of interest to report and briefly discuss two cases of sickle-cell anemia in infants recently admitted to the pediatric service of the University Hospital.

CASE REPORTS

Case 1.—W. M., a 3-month-old Negro male infant, was admitted to the pediatric service on Sept. 1, 1949, because of marked anemia and weakness. He had been delivered at home by a midwife. At birth he was said to have had water blisters on his body. He was placed on a weak evaporated milk formula, but despite this, he had persistent vomiting. The vomiting, however, was not projectile. He was carried to a physician at the age of one month and at that time he was placed on an adequate evaporated milk formula. He had been receiving no additional vitamins or orange juice. At the age of one week, he was said to have had a mild convulsion. He developed a diarrhea several days before admission and was given some medicine by a physician. He became progressively weaker and was sent to this hospital in a very weakened condition. Family history revealed that his father and mother were living and well. There were no siblings. There was no history of any anemia in the family.

Physical Examination.—He had a temperature of 101° F., a pulse of 160 per minute, and a respiratory rate of 60 per minute. He was a fairly well-nourished and well-developed Negro male infant who appeared quite weak. He was not alert and did not respond well. There was marked pallor of the mucous membranes. The palms of the hands and the soles of the feet were white. There seemed to be some pain on pressure over the long bones. He was having marked respiratory distress, although there seemed to be no obstructive element present. The lungs were clear. The heart was slightly enlarged on percussion. The rate was rapid and regular. There was a blowing systolic murmur heard throughout the precordium. The liver edge was palpable. The spleen could not be palpated.

Laboratory Studies.—The urine was negative. The red cell-count was 1,170,000 with 2.7 Gm. Hb. The white cell count was 25,600, 65 per cent of which were nucleated red cells. The red cells sickled immediately on the smear and on a wet preparation. There was about 95 per cent immediate sickling present. The blood serology was negative.

On admission it was felt that this patient was in impending shock. Therefore, immediate oxygen therapy was administered and a blood transfusion was given within two hours after admission. During the transfusion the patient showed marked improvement. He was given two other transfusions of whole blood and each transfusion brought about marked improvement in the patient's condition. He was dismissed six days after the date of admission with a diagnosis of sickle-cell anemia.

CASE 2.—C. S., a 7-month-old Negro male infant, was admitted to this hospital on Sept. 19, 1949, with a mass in the left side of his abdomen plus a marked anemia. This mass was first noticed by the grandmother ten weeks previously when he was 4½ months of age. This mass seemed to get larger. He was taken to a physician who noted the mass and found the hemoglobin to be 4.6 Gm. He had not been nursing or eating well and had been losing some weight. He was given some iron and vitamins, plus a large dose of vitamin B_{12}. One week later the hemoglobin was down to 4.1 Gm. The referral diagnosis was splenic anemia.

History.—The past history revealed a normal birth and development except for being small for his age. He was trying to sit up at 7 months of age despite his weakness. He had had no previous illnesses and received no immunizations. The family history revealed that the mother had only recently been placed in a mental institution. The health of the father was unknown. There was no definite history of anemia or any familial disease.

Physical Examination.—He had a temperature of 100° F., a pulse of 132 per minute, and a respiratory rate of 36 per minute. He was a fairly well-developed, but slightly undernourished Negro male infant, who appeared alert, but somewhat weak. The palms of his hands and soles of his feet were whitish. Mucous membranes were quite pale. No icterus was noted in the sclera. He was well hydrated. The chest was clear and the heart seemed slightly enlarged on percussion. There was a slight systolic murmur which was best heard at the apex. The abdomen protruded somewhat. The distention seemed more prominent in the upper portion. The spleen was markedly enlarged, the lower edge being below the level of the umbilicus. It was freely movable on respiration and palpation. The liver edge was about 2 cm. below the subcostal margin.

Laboratory Studies.—Various laboratory studies were performed. The urine was negative. There was no bilirubin in the urine and the urobilinogen was normal. On admission the blood showed 1,150,000 red cells with 4 Gm. Hb. The original white blood count was 48,850, 87 per cent of which were nucleated red cells. The true white count was 6,350 with a differential of 68 per cent polymorphonuclears, 28 per cent lymphocytes, and 4 per cent monocytes. There was some basophilic stipling, and sickling of the red cells was immediate. Ninety per cent of the red cells sickled immediately. This immediate sickling was demonstrated on both the smear and a wet preparation. The color index was 1.19. Fragility test revealed decreased hemolysis to hypotonic saline solution. The platelet count was 233,510. The bleeding time was 1.5 minutes and the clotting time was 3 minutes. The prothrombin time was 18.5 seconds by the Quick method. The blood serology was negative. Further blood studies after transfusions revealed a hemoglobin of 9.5 Gm. and the nucleated red cells being only 38 per cent of the total white count.

After the laboratory studies were made in order to substantiate the diagnosis, this patient was transfused with whole blood on several occasions. The patient showed marked improvement and there was a noticeable decrease in the size of the spleen. He was dismissed on Sept. 27, 1949, with a diagnosis of sickle-cell enemia.

DISCUSSION

Sickle-cell anemia is a congenital, mendelian dominant anemia which is mostly found in the Negro race. There have been a few cases found in the Mediterranean peoples! In this disease the red blood cells assume a characteristic sickle shape which is usually seen immediately on smears or wet preparations. This peculiar characteristic of sickling of the erythrocytes is easily demonstrated on a blood smear stained with Wright's stain. It is better produced by placing a small rubber band around the finger and after three minutes collecting a drop of blood on a cover, which is then sealed with petroleum jelly on a slide. There is a variety of symptoms which are found in sickle-cell anemia. There is usually a marked anemia, jaundice, splenomegaly, and symptoms of pain in the extremities or in the abdomen during a crisis. This condition should not be confused with "sicklemia," which has latent sickling of the erythrocytes, but has no symptoms. This is found in about 8 per cent of the Negro population. These two conditions may be the same disease; the difference being in the tendency of the red blood cells to sickle more easily and thereby cause trouble in the "active" sickle-cell anemia.

Sickling of erythrocytes is brought about by having the trait existing and a condition that produces hypoxia. In the absence of sufficient oxygen, these cells assume this sickle shape. Pauling and co-workers[6] have recently made some remarkable findings which may lead to a better understanding of why some individual's erythrocytes will sickle and those of others do not. They demonstrated an actual physical difference in the positive charges of the molecules of the hemoglobin in erythrocytes of normal individuals and those of sickle-cell anemic individuals. The globins rather than the hemes of the two hemoglobins seemed to be different. This "defective" hemoglobin of sickle-cell anemia aggregates into one or more locations within the cell membranes thereby causing the membranes to collapse and produce hemolysis. These "defective" hemoglobin molecules of sickle-cell anemia are found in erythrocytes of individuals with sicklemia along with normal hemoglobin, but there is more abnormal hemoglobin in proportion found in the erythrocytes of individuals with sickle-cell anemia.

The anemia found in sickle-cell anemia is usually fairly marked. In both cases in this paper as well as in most cases, this was found to be true. This is usually a normocytic type of anemia, but anisocytosis and poikilocytosis are quite common. Usually the color index is less than one. During a crisis large numbers of normoblasts are found in the peripheral blood, and reticulocytosis is common. Unfortunately an accurate reticulocyte count was not obtained in either of the two cases reported in this paper. Despite this being a hemolytic disease, there is usually a decreased hemolysis of the red blood cells with hypotonic saline. In splenic anemia and other types of hemolytic anemia there is

usually an increased hemolysis on a fragility test determination. The jaundice that is commonly seen in sickle-cell anemia was not found in these two cases.

The existing anemia causes extreme weakness. In addition the heart is usually dilated as in most profound anemias. There is usually a systolic murmur at the apex which represents relative mitral insufficiency. This anemia produces an hypoxia which helps to cause further sickling. The tissue ischemia from the hypoxemia and from the clumping together of these abnormally shaped red cells in the capillaries causes pain wherever this process occurs. Usually there are symptoms of abdominal pain or discomfort in the extremities. The spleen is commonly enlarged in sickle-cell anemia, although this is not a constant finding. In the first case described here, the spleen could not be palpated.

Unsuccessful attempts were made to study the blood of the parents of these two patients. In the first case, the parents were not cooperative and in the second one the parents were not available. However, it is felt that these patients definitely had sickle-cell anemia which was manifested early in infancy. The first case was diagnosed at the age of 3 months. The second patient was admitted at the age of 7 months, but the condition of sickle-cell anemia had actually existed at the age of 4½ months. It is interesting to note that these two cases of sickle-cell anemia in young infants were in patients admitted within a few days of each other.

It is felt that many more cases of sickle-cell anemia in infants would be found if a sickle-cell preparation is performed on all Negro infants and children who have any anemia or have any obscure signs or symptoms. At the University Hospital we routinely obtain a sickle-cell preparation on all Negro patients who are admitted to the pediatric service. By doing so, we have found quite a number of individuals with latent sickling of their red blood cells and occasionally we find one with early sickling. We believe that this is a valuable diagnostic laboratory procedure that should be incorporated into the other common laboratory procedures.

SUMMARY

1. Two cases of sickle-cell anemia in young infants are reported.

2. The relationship between sickle-cell anemia and sicklemia is discussed briefly.

3. A short review of the findings in sickle-cell anemia is made.

4. These cases seem to indicate that there may be more cases of sickle-cell anemia found in infants if a sickle-cell preparation is performed routinely on all admissions of Negro infants and children to hospitals and in office practice. It should especially be done on all Negroes with any anemia.

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CONGENITAL MALFORMATIONS WITH SEVERE DAMAGE TO THE CENTRAL NERVOUS SYSTEM DUE TO EARLY FETAL VIRUS INFECTION

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THE suggestion of Gregg,[1] in 1941 that a causal relationship existed between maternal rubella during the early months of pregnancy and congenital cataract in the offspring, aroused widespread interest as well as serious skepticism. During the eight years that followed, many publications on this subject appeared in the Australian, American, and European literature.[2-17] Beyond doubt the fact has been established that maternal rubella and some other virus infections during the first three months of gestation may cause characteristic congenital malformations in the human fetus. Embryologic studies have proved that various congenital malformations can be experimentally produced in vertebrates and in mammals.[19, 22] This has been achieved by nutritional deficiencies, and by chemical, thermal, and mechanical lesions which affect the embryo at closely defined early stages of development. These "experimental malformations" often accurately simulate those usually considered genetic and hereditary in origin. Further, it was shown that environmental disturbances have the same "pleiotropic" effect, producing multiple malformations, as abnormal genetic factors. A survey of the latest developments in experimental embryology can be found in a recent publication by Werthemann.[23]

Gregg's discovery that a maternal virus infection could cause severe damage in the fetus was not as new as it first appeared. The experience that undifferentiated embryonic tissue is especially susceptible to virus infections has long been used in the laboratory: viruses are grown on the chick embryo for experimental and therapeutic purposes. It has long been known that maternal infection with smallpox, influenza, measles, and poliomyelitis may cause abortion or stillbirth. With smallpox the rate of abortion was 80 per cent. During the great pandemic of virus influenza in 1918, many prospective young mothers who acquired the disease died or aborted a dead fetus, regardless of the period of gestation.

The fourth to the tenth week of pregnancy appears to be the critical period for an effective attack on the lens, the heart, and the ear of the fetus. At this time the placental barrier is still vulnerable and these organs are in their most active stage of differentiation. Rubella, after the termination of organogenesis, from the fourth fetal month, does not produce germinal damage.[23] It may, however, cause stillbirth or congenital rubella.

At present the following congenital malformations, which may be solitary or in combination, are generally considered characteristic of maternal rubella. They have also been reported after maternal influenza and mumps: (1) congenital cataract of a specific type; (2) congenital malformation of the heart, mostly septum defect or patent ductus Botalli; (3) deaf-mutism; (4) feeding

difficulties with retarded physical development; (5) microcephaly; (6) disturbances of dentition, such as delayed teething, hypoplasia, and anomalies in form and position of the teeth; (7) mental deficiency.

Little is known as yet of the prognosis of those children injured in fetal life by maternal rubella. As Gregg says: "It is difficult to forecast the future for these unfortunate babies. We cannot, at this stage, be sure that there are not other defects present which are not evident now but which may show up as development proceeds. The cardiac condition also tends to make the prognosis doubtful. The possibility of the appearance of neurotropic manifestations at a later date will be kept in mind. The prognosis for vision depends on the presence or absence of nystagmus and the condition of the retina and choroid."

The present study is a contribution to the problem of congenital defects in children due to virus infections in the pregnant mother from the Dixon and Lincoln State Hospitals of Illinois. Special attention was given to the possible causative relation of influenza and the common cold in congenital malformations and to the search for later neurotropic manifestations which could not be observed in the original material of a group of young infants. Furthermore, it was hoped that the observation of institutional patients over many years would allow some conclusions as to the prognosis in their physical and mental development.

Studies from institutions for the feeble-minded must of necessity describe children with severe injury, since all are suffering from severe mental deficiency. It is therefore not remarkable that the patients described have many defects and an unusually dark prognosis.

The children studied were those who suffered from congenital malformation of the eyes with at least one other congenital defect. The history taken on admission was elaborated with special attention to details of the pregnancy, the delivery, and the family inheritance of defect.

It was soon realized that the most difficult task in this study was to obtain an accurate history. It is obviously hard for a mother to remember, after many years, the exact time of onset and the details of some mild illness. Only two of the patients referred to in this paper were committed to the State Hospital at Dixon with a history of their mothers having had rubella in the first three months of the pregnancy.

Questionnaires were sent to the mothers of the remaining children. They were all answered in the negative. Personal interviews with the mothers were then arranged. These mothers were asked to try to remember all the details of the early months of the pregnancy and to discuss them with and inquire about them from their husbands, parents, and friends. This system finally produced results.

In one case where the child had a combination of all the typical rubella defects and where the first months of gestation coincided with the Illinois epidemic of German measles in 1942, the mother had twice assured me of her perfect well-being throughout the pregnancy. On a third visit, she said her own mother, with whom she had lived at that time, remembered this epidemic. Only then had she herself recollected the red spots on her face, which appeared before the end of the third month of her pregnancy and lasted only for three days. These

spots had worried her because she had always had such a clear complexion. Other women recollected the dates of their illness in connection with trips to military camps where their husbands were then stationed, with Fourth of July celebrations, or other impressive happenings. Since, unfortunately, personal contacts were not possible with the mothers of the patients from the Lincoln State Hospital, only two Lincoln patients against fourteen Dixon patients were used in this study.

The remarkable discrepancy between results in the questionnaire method and the personal interview method would show that negative answers in questionnaires should not be regarded as conclusive.

Since a detailed report of the history, signs, and development in the children who were subjects of this study would take too much space, the most important findings are condensed in two tables.

Table I consists of seven cases of children in whom maternal rubella during the first three months of pregnancy was certain, and of three similar cases with unknown etiology. In addition to the "classical" postrubella syndrome appearing in Columns 3 to 7 of this table, Column 8 shows an unusual variety of neurological signs which characterize the seriously damaged institutionalized children.

Among the six children of Table II, the first case is attributable to virus influenza and the remaining five to severe common colds within the first three months of gestation. In contradistinction to the congenital cataract and microphthalmia characteristic of postrubella cases, these children present more unusual congenital defects of the eye: three are suffering from buphthalmos or macrophthalmia and two from complete agenesia of the eyeballs. These two rare cases will be published in detail in a separate paper. The neurological signs are similar in both groups.

COMMENT

From the children and infants of the Dixon and Lincoln State Hospitals, sixteen patients were studied who showed congenital malformations resembling the "postrubella" syndrome. The important data concerning their histories, physical findings, and development up to the ages of 3 to 10 years were condensed in two tables.

As to the etiology, the most interesting result was that in five patients the congenital malformations were attributable to severe common colds within the first three months of gestation.

As to the symptomatology, the institutionalized children presented in this article exhibit all the manifestations of unusually severe damage to the fetus. Severe mental deficiency was present in all the sixteen patients, two were imbeciles, the other fourteen were idiots. Most probably their failure to develop normal mentality is not due only to their blindness and complete or partial deafness, but to an associated failure in normal cortical development. This defect may result from an intrauterine meningo-encephalomyelitis or from an arrest in development from the period of the maternal infection.

No complete neuropathologic examination of the effects on the growing brain of such maternal infection has yet been reported, although some are in processes of study.

TABLE I. MATERNAL RUBELLA CERTAIN OR PROBABLE DURING FIRST THREE MONTHS OF PREGNANCY

ORDER AND TERM OF BIRTH, WEIGHT, DELIVERY, SIBLINGS	MATERNAL VIRUS INFECTION	CONGENITAL EYE DEFECTS	CONGENITAL HEART DEFECT	HEARING	MICRO-CEPHALUS	FEEDING PROBLEM	MENTAL DEFICIENCY, NEUROLOGICAL SIGNS, AND OTHER ABNORMALITIES
1. P. B., second child, 2-3 week premature, 4 pounds 10 ounces. Normal delivery, 1 older and 1 younger normal sibling	Rubella during sixth week of pregnancy	Bilateral congenital cataract, microphthalmia, horizontal nystagmus. Only light perception	Systolic and diastolic murmur. Patent ductus arteriosus and malformation of aortic valve	Normal	Pronounced. Flat occiput. Circumference 16¾ inches at 4½ years	Extreme. Weight 20 pounds at 5 years	Severe mental deficiency, I.Q. 8. Pronounced hypotonia of legs with hyperactive deep reflexes, spontaneous Babinski. Narrow palate, disturbance of dentition. Large protruding ears, mild arachnodactylia, severe chronic microcytic anemia
2. L. D. S., first child, full term, weight only 4 pounds 13 ounces. Normal delivery. 1 younger sibling of superior intelligence	Rubella during the sixth week of pregnancy	Bilateral congenital cataract; microphthalmia, convergent strabismus right eye, horizontal and rotating nystagmus, poor vision	None	No reaction to sounds	Moderate degree. Flat occiput. Circumference 18 inches at 5½ years	None	Severe mental deficiency, hyperactive idiot, I.Q. 15. Transitory hypertonia of her arms. Screaming spells; irritable, aggressive, and mean toward other children
3. W. B. C., first child, 2 weeks early, 5 pounds, 10 ounces, easy delivery. 1 younger sibling normal	Rubella at beginning of third month of pregnancy	Dextroversion, horizontal nystagmus. Beginning optic atrophy, residues of old choreoiditis. Poor vision	None	Partially deaf	Mild degree. Circumference 19¼ inches at 6½ years	None	Severe mental deficiency, I.Q. 4. Moderate spasticity, more on left side. Spontaneous Babinski left side, mild foot clonus both sides. Tonic convulsions at 2 years and 3 years. Disturbance of dentition, large protruding ears, undescended testicles at 7 years. Operated pyloric stenosis
4. J. McC., second child, full term, 5 pounds 13 ounces. Easy delivery, 1 older sibling normal	Rubella during third month of pregnancy	Bilateral congenital cataract; left microphthalmia, incoordinated eye movements, horizontal nystagmus. Blind	None	No reaction to sound	Moderate degree. Circumference 18 inches at 5 years	None Weight 35 pounds at 6 years	Severe mental deficiency, I.Q. 10. Mild spasticity of right leg with hyperactive deep reflexes and patellary clonus. Deformed protruding ears. Unusually long big toes

5. V. A. S., second child, full term, 7 pounds 9 ounces. Forceps, 1 older and 1 younger sibling normal	Rubella during second month of pregnancy	Bilateral congenital cataract; microphthalmia, horizontal and rotating nystagmus. Blind	Loud blowing systolic murmur, no cyanosis	No reaction to sound	Pronounced. Flat occiput. Circumference 18 inches at 5½ years	Extreme. Weight 20 pounds at 5½ years	Severe mental deficiency, I.Q. 15. Pronounced spasticity of both legs with contractures of knee joints. Babinski on right side. Disturbance of dentition. Deformed left ear
6. J. D., third child, twin 6½ months gestation, 2 pounds 9½ ounces. Easy spontaneous delivery. 2 older and 4 younger normal siblings	Rubella during second or third month of pregnancy	Bilateral congenital cataract. Blind	None	No reaction to sound	Moderate degree. Flat occiput. Circumference 18 inches at 5 years	Severe. Weight 28 pounds at 6 years	Severe mental deficiency, I.Q. 8. Moderate spasticity of all four extremities, hyperactive deep reflexes, Babinski and ankle clonus on left side. High arched narrow palate
7. D. B. R., second child, 7 months premature, 3 pounds 8 ounces. Spontaneous delivery. 1 older and 1 younger sibling normal	Rubella during early months of pregnancy almost certain	Bilateral congenital cataract; microphthalmia. Glaucoma of right eye at 1½ years	Loud blowing systolic murmur, heart enlarged, no decompensation	No reaction to sound	Pronounced. Flat occiput. Circumference 18 inches at 5½ years	Severe. Weight 27½ pounds at 6 years	Severe mental deficiency, I.Q. 7. Moderate degree of hypotonia of all four extremities. Spontaneous Babinski on both sides
8. A. D., fourth child, full term, difficult instrumental delivery. 3 older and 2 younger siblings normal	Rubella probable but not remembered	Bilateral congenital cataract; nystagmus. Blind	None	Partially deaf	Moderate degree. Flat occiput. Circumference 18¾ inches at 5½ years	Severe	Severe mental deficiency, I.Q. 12. Hyperactive deep reflexes and Babinski. Frequent convulsions from birth, later only attacks of petit mal
9. J. G., fifth child, full term, 6 pounds 2 ounces. Normal spontaneous delivery. 4 older and 3 younger siblings are normal	Mother does not remember any illness during pregnancy	Bilateral congenital cataract; microphthalmia. Only light perception	None	Normal	Moderate degree. Circumference 17¾ inches at 8 years.	Moderate degree. Weight 32 pounds at 8 years	Severe mental deficiency, I.Q. 16. Mild spasticity of both legs with hyperactive deep reflexes. High arched palate with disturbed dentition
10. B. M., foundling. Born 1-29-42. History unknown	Unknown	Bilateral congenital cataract; horizontal nystagmus. Blind	None	No reaction to sound	Pronounced. Circumference 17¾ inches at 6½ Years	Extreme weight 22 pounds at 6½ years	Severe mental deficiency, I.Q. 10. Moderate spasticity of both arms and legs with hyperactive deep reflexes. Mild degree of arachnodactylia

TABLE II. INFLUENZA OR SEVERE COMMON COLD DURING FIRST THREE MONTHS OF PREGNANCY

ORDER AND TERM OF BIRTH, WEIGHT, DELIVERY, SIBLINGS	MATERNAL VIRUS INFECTION	CONGENITAL EYE DEFECTS	CONGENITAL HEART DEFECT	HEARING	MICRO-CEPHALUS	FEEDING PROBLEM	MENTAL DEFICIENCY, NEUROLOGICAL SIGNS, AND OTHER ABNORMALITIES
11. T. K., first child, full term, 7 pounds 11 ounces. Easy spontaneous delivery. 1 younger sibling normal	Severe virus influenza through first and second month of pregnancy	Bilateral congenital buphthalmos, convergent strabismus, horizontal nystagmus. Bilateral optic atrophy with restricted visual field	None	No reaction to sound	Mild degree. Circumference 18¼ inches at 2½ years	Severe. Weight 20 pounds at 2½ years	Severe mental deficiency, I.Q. 12. Mild spasticity of left arm and leg with hyperactive deep reflexes. High arched narrow palate, disturbance of dentition. Large deformed ears. Undescended right testicle
12. C. R. Sp., first child, full term, 5½ pounds. Spontaneous delivery. No siblings	Terrific cold at the beginning of third month of pregnancy	Bilateral buphthalmos, horizontal nystagmus, very poor vision	Loud blowing systolic murmur, heart enlarged. No cyanosis	Normal	Pronounced. Circumference 16 inches at 7½ years	Mild degree. Weight 36 pounds at 7½ years	Severe mental deficiency, I.Q. 35. Hyperactive deep reflexes, queer hopping gait. High arched palate, disturbed dentition
13. M. N., second child, full term, 7 pounds 6 ounces. Spontaneous delivery. 1 older and 1 younger sibling normal	Severe cold with keratoconjunctivitis during second month of pregnancy	Complete agenesia of both eyeballs with rudimentary eyelids and palpebral fissures	None	No reaction to sound	Square head. Circumference 19 inches at 4½ years. Flat occiput. Platybasia and persistent parietal foramina	Severe dystrophy in spite of excellent appetite. 27 pounds at 6 years	Severe mental deficiency, I.Q. 14. Pronounced hypotonia of all four extremities with absence of deep reflexes. High arched palate and extremely narrow lower jaw with disturbance of dentition. Large deformed ears. Small scrotum and undescended testicles at 6 years

14. J. N., first child, full term, 5 pounds 8 ounces. Easy spontaneous delivery. No siblings	Severe sore throat during first month of pregnancy	Moderate degree of macrophthalmia and unusual amount of retinal pigment	None	Normal	Moderate degree. Circumference 18 inches at 4½ years	Severe. Weight 33 pounds at 5 years	Severe mental deficiency, I.Q. 24. Hyperactive and destructive
15. J. H. E., first child, 7 months' gestation, 3 pounds 10 ounces. Easy spontaneous delivery. 1 normal younger sibling	Severe head and chest cold at beginning of second month of pregnancy	Bilateral congenital cataract; microphthalmia. Blind	None	Normal	Large scaphocephalic head. Hydrocephalus? Circumference 22¾ inches at 4½ years	Extreme. Weight 13 pounds at 2 years	Severe mental deficiency. Pronounced spasticity of all four extremities with contractures. High, arched narrow palate with disturbance of dentition. Large deformed ears
16. W. M. A., first child, full term, 7 pounds 14 ounces. Normal spontaneous delivery. 3 younger siblings are normal	Quite a number of bad colds during pregnancy, exact time unknown	Complete agenesia of both eyeballs with rudimentary eyelids and palpebral fissures	None	No reaction to sound	Square head with flat occiput and platybasia	Moderate degree	Severe mental deficiency. Pronounced hypotonia of both legs with absence of deep reflexes. Large deformed ears. Undescended testicles. Terminal illness with convulsions and hyperthermia of 108 degrees F. Autopsy showed sclerosis of the brain, microgyria of both occipital lobes and uncrossed optic nerves

If there were not an associated cerebral dysgenesis, it would be difficult to explain why microcephalus is the second in frequency among the congenital defects in this series, being present in thirteen patients. Furthermore, of the six children who were not deaf, only two learned to talk, and of the seven who were not blind, only three showed some interest in their surroundings. This low mentality and high incidence of microcephalus is in contrast to children described from institutions for the deaf. Those children were mentally normal and, apart from their hearing defect, showed almost no other congenital malformations. These different experiences would prove that our group of children is a special selection of seriously damaged children, and that the same virus infection, in fetal as well as in postnatal life, may produce a wide range of defects. The results may vary from abortion to stillbirth and more or less severe congenital defects to normal children.* Whether the time of infection or the "genius epidemicus" of a certain epidemic, or other still unknown factors are most important in this respect is yet uncertain. There is, however, no correlation between the severity of the maternal illness and that of the fetal damage.

Severe feeding difficulties and pronounced retardation of physical development with twelve patients each range third as to frequency. There is almost no other disease entity in which such severe dystrophies are seen. Body weights of between 20 and 25 pounds at 5 years of age are not unusual in this group of children. Some of them get no enjoyment from food and practically every meal has to be forced. Others who eat better and a few who enjoy five big meals daily, nevertheless do not put on much weight. None of these children is cooperative enough to undergo a metabolic test. However, from the frequency and severity of this nutritional and growth disturbance, it may be assumed that it is due to some central damage. From the low birth weights of many of our patients it would appear that this damage is already active during fetal life.

Deaf mutism ranged fourth as to frequency with eleven patients, and congenital cataracts range fifth with ten of sixteen patients. Less frequent abnormalities of the eyes were microphthalmus in eight patients; buphthalmos in three patients—all of them after influenza or common colds; complete agenesia of the eyeballs in two patients; optic atrophy in two patients and residual chorioretinitis or abnormal pigmentation of the retina in one patient each.

Disturbance of the teeth such as late beginning of dentition and poor quality of teeth were noticed in seven patients. These were mostly associated with a high-arched, narrow palate. Congenital malformation of the heart was observed in only six patients. Eight of our children had large, deformed ears.

Since the institutionalized children described in this paper suffered unusually severe damage to the central nervous system, it is not remarkable that some exhibited neurological signs which had not been described before in postrubella cases. Eight children showed spasticity of their extremities which was of mild or moderate degree in 6 and severe with contractures in 2. In 2 additional patients only hyperactive deep reflexes and spontaneous Babinski

*The Australian authors, according to their last follow-up report in 1946, found only two normal children among sixty-two whose mothers had rubella during the first two months of their pregnancy.

without spasticity were observed. Only one of the severe spastics was a forceps delivery, but did not show any signs of birth injury during the neonatal period. All the other spastics were by normal, easy deliveries. Four patients showed definite hypotonia, among them the 2 rare cases of complete agenesia of the eyeballs. Twice this hypotonia was associated with hyperactive deep reflexes and spontaneous Babinski, whereas in both patients with agenesia of the eyeballs the deep reflexes were absent. Convulsions of grand mal type were observed in 3 of the Dixon patients, whereas petit mal or jerking spells are mentioned in the 2 Lincoln patients.

What is the relative frequency and importance of postinfectious congenital malformations as compared to other malformations whose origin is still unknown? In order to get an approximate idea as far as the Dixon patients are concerned, the following statistical study was made: In our present group of 252 children of preschool age, from which the subjects of this study were chosen, there were 118 children with congenital malformations not due to birth injury, postnatal injury, postnatal infection, or known hereditary factors. These children consisted of 46 Mongols, 27 with microcephalus, 13 with hypdrocephalus or other malformations of the head with or without spina bifida, 14 children with cerebral agenesia, 7 with multiple malformations, and 11 various rare cases. Since most children with severe cases of hydrocephalus and meningocele and a high percentage of the Mongols die soon after admission, whereas the postrubella patients live for many years in spite of their severe dystrophies, we added to the 118 living patients with malformations those 102 patients with congenital malformations of unknown origin who had expired in our children's hospital since 1945. Compared to these 220 congenital malformations of unknown etiology, the 14 cases due to maternal and most probably to early fetal virus infection would make roughly 6 per cent. This agrees well with statistics from Sweden by Gronvall and Selander[21] in which the authors found about 5 per cent of 354 congenital malformations of heretofore unknown etiology attributable to maternal virus infection during pregnancy.

Much remains to be done before all the problems dealt with in this paper will be solved. Our present knowledge, scarce as it is, should be spread to every person working in the field of public health and public welfare. The entire population should be stimulated to help in the prevention of virus infections during the early months of pregnancy.

SUMMARY

1. Among 16 institutional patients with congenital malformations resembling the postrubella syndrome, a history of maternal rubella was found in 7 cases. Most likely a severe common cold within the first three months of gestation was the causative factor in 5 cases and virus influenza in 1 case.

2. The ocular defects due to virus influenza or the common cold during early fetal life appear to differ from those in postrubella patients.

3. In addition to the "classical" postrubella defects, the institutionalized children of this study present an unusual variety of neurological signs: 8 children show spasticity of their extremities, 4 exhibit definite hypotonia with

hyperactivity or absence of the deep reflexes. Convulsions of grand mal type were observed in 3 patients, jerking spells or petit mal seizures occurred in 2 additional patients.

4. Approximately 6 per cent of the institutionalized children with congenital malformations of heretofore unknown etiology may be attributable to early fetal virus infection.

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REACTIVATION OF RHEUMATIC FEVER BY SMALLPOX VACCINATION

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IN New York City during April, 1947, there occurred several cases of smallpox that were followed by the vaccination of a large percentage of the city population. Practically all children who had not been vaccinated for a period of two or three years were revaccinated. The few well-known and often stressed contraindications such as eczema, various other types of dermatitis, and debility were generally observed.

Following the accepted medical procedure, almost all the children in the pediatric service at Metropolitan Hospital were vaccinated. Among these were five children with rheumatic fever. Because of the definite reactivation of two of these cases and the probable reactivation of two others following vaccination, our attention was focused on the possible danger presented by this procedure. Two similar cases were seen by one of us (P. F.) on the outside at the same time.

A thorough search of the literature was then made to determine the known facts on the relationship of smallpox vaccination to rheumatic fever. There were many contradictory reports on the influence of vaccination on the course of tuberculosis, some stating that vaccination was deleterious,[2] others maintaining that the procedure was entirely harmless,[1, 3, 4, 6, 7] but as far as could be determined nothing has been written concerning the possible relationship of smallpox vaccination to rheumatic fever. There was, however, an article on reactivation of rheumatic fever by the injection of typhoid vaccines.[8] In addition, L. Taran[10] observed two and possibly three patients with inactive rheumatic fever who developed chorea shortly after being vaccinated against smallpox.

The following case reports suggest that smallpox vaccination can cause reactivation of rheumatic fever. Of the five patients in the hospital, four are described, two with definite reactivation of the disease (Cases 3 to 6) and two concerning whom there is some doubt as to the sequence of events leading to recurrence (Cases 5 and 6). The fifth (Case 7) showed no reactivation. Of six carefully observed rheumatic fever cases on the outside, two (Cases 1 and 2) became active following vaccination while in four others (Cases 8 to 11) there was no detrimental effect.

CASE REPORTS

CASE 1.—G. L., a 10-year-old white girl, was first seen at the age of 7 years for a rheumatic polyarthritis and carditis. The rheumatic episode followed an upper-respiratory infection and had started with fever and repeated epistaxis. On the tenth day of illness the sedimentation rate was 54 mm. per hour (Westergren) and the hemogram showed red blood cells 3,700,000, hemoglobin 69 per

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cent, white blood cells 11,250 with 76 per cent polymorphonuclears. The polyarthritis responded well to salicylates, and after three months of bed rest the clinical and laboratory evidence of activity had disappeared. The sedimentation rate was 11 mm. per hour, the red blood count had risen to 4,100,000, the hemoglobin to 79 per cent, and the white blood count was now 7,200 with a normal differential count. On auscultation an apical systolic murmur and an accentuated second pulmonic sound were heard. X-ray revealed mitralization of the heart.

As soon as it was certain that the disease was quiescent, the child was placed on prophylactic sulfadiazine 0.5 Gm. twice daily. Urinalysis and blood counts were done periodically.

The child did well for one year when suddenly, following a sore throat she suffered another attack of polyarthritis. This time it was two months before everything returned to normal. X-ray and clinical examination revealed no further damage to her heart. For the following two years the child did well. She had occasional colds but never were they followed by any rheumatic manifestations.

The child had been vaccinated at the age of 6 months and was revaccinated on April 23, 1947. She was then 10 years old and in excellent condition. Her mother stated that she had had no colds that winter. The physical examination at the time of vaccination was entirely negative except for the heart findings, which were unchanged.

The vaccination took and there was development of a typical primary vaccinia with a temperature rise to 101.2° F. on the tenth day. There was no fever the following day but the child looked quite pale and complained of fatigue. Her mother reported that the girl seemed quite nervous during the next few days, that she cried for no reason whatsoever and did not want to go to school. A week after vaccination the teacher communicated with the mother concerning the changed behavior of the girl, who disturbed the class with outbursts of unmotivated crying and laughing. She was sent home from school and put to bed. The next day she ran a temperature of 100.8° F. and at that time the diagnosis of chorea was made. The sedimentation rate done that same day was normal, but her white blood count was 9,800 with 78 per cent polymorphonuclear cells. Despite sedatives and bed rest, there were increased involuntary jerky movements, definite muscular weakness of the right arm and hand, and quite pronounced emotional instability.

This condition remained the same for two weeks. At that time the temperature went up to 102.3° F. A double murmur developed over the mitral region and gallop rhythm was present.

The blood count was red blood cells 3,900,000, hemoglobin 73 per cent, white blood cells 11,450, 79 per cent polymorphonuclear cells with many young forms. The sedimentation rate had gone up to 54 mm. per hour (Westergren). The signs of chorea decreased gradually after about eight weeks and after four months of bed rest the temperature, the sedimentation rate, and the white blood count returned to normal.

Following this rheumatic attack, the heart of the child remained enlarged and there was a typical double murmur over the mitral region.

Since then the child, who is now 12 years of age, has had no reactivation of her rheumatic condition.

CASE 2.—C. S., a 9-year-old white boy, had a first episode of rheumatic fever at 7½ years of age. At this time there was considerable painful swelling of the left ankle with marked redness extending up over the lower part of the tibia, so that a tentative diagnosis of osteomyelitis was first entertained. How-

ever, after a few days other joints became involved, and systolic and presystolic murmurs developed. The temperature remained high (102° to 103° F.) and the sedimentation rate was 78 mm. per hour (Westergren). The white blood counts ranged from 10 to 12,000 with polynucleosis and shift to the left, and red blood count and hemoglobin decreased to 2,900,000 and 69 per cent, respectively. Joint pains and swelling responded well to salicylates, and x-ray studies of the left ankle and other involved joints remained negative.

After eight weeks of bed rest, all signs and symptoms of activity had disappeared. The sedimentation rate was 12 mm. per hour at this time and the child was permitted to gradually return to full activity. The heart findings remained unchanged.

One month afterward, the chronically inflamed tonsils were removed and two carious teeth were extracted. The child was started on 0.5 Gm. of sulfadiazine twice daily and was sent to the country for three months. Following this period of convalescence the child returned to school and participated in all activities except competitive sports. For the next one and one-half years there was no recurrence.

In April, 1947, the child, who had been vaccinated in infancy, was revaccinated. A typical primary vaccinia developed after one week. There was no fever. Two days later a scab had formed on the vaccination. That same evening the child complained of severe abdominal pains and vomited repeatedly. The temperature rose to 104° F.

The blood count done on the following day showed white blood cells 22,300, with 78 per cent polymorphonuclears and a shift to the left. The sedimentation rate was 69 mm. per hour. Four days after this abrupt onset the right elbow became swollen and painful and within a few days other large joints became involved. Occasionally gallop rhythm was heard on auscultation of the heart.

Not until eight months later did the clinical and laboratory findings return to normal. Cardiac examination at this time revealed findings similar to those before reactivation: a double murmur with moderate enlargement to both the right and left.

CASE 3.—R. D., a 10-year-old Puerto Rican girl, was admitted to Metropolitan Hospital on March 5, 1947, because of swelling of the right knee and ankle. She gave a past history of frequent sore throats and an attack of rheumatic fever at the age of 8 years. There was also a questionable history of chorea at about the same time. On admission the only significant findings on physical examination were the swollen, tender right knee and ankle, and systolic and presystolic apical murmurs. X-ray of the chest was reported as revealing a globular heart, while the fluoroscopy was suggestive of an enlarged left auricle and right ventricle. The electrocardiogram on two occasions demonstrated only sinus tachycardia. The sedimentation rate was 30 mm. per hour (Westergren), and the hemogram showed red blood cells 5,000,000, hemoglobin 12.5 Gm., white blood count 13,950 with 56 per cent polymorphonuclears, and 44 per cent lymphocytes.

By the fifth hospital day the joints appeared to be normal. However, the heart findings were unchanged and remained so throughout hospitalization. The sedimentation rate, after an initial rise to 45 mm. per hour on March 19, returned to normal (April 1, 35 mm.; April 7, 23 mm.; April 16, 18 mm., all with Westergren tubes). The child was vaccinated against smallpox on April 14 with a positive take, and by April 23, the sedimentation rate was 60 mm. On April 28, it was 90 mm. per hour. The heart rate was rapid and the sounds were of poor quality, although the temperature remained low. It was not until June 10 that the sedimentation rate was once more normal. The child was dis-

charged June 15, 1947. (Sedimentation rates: May 7, 50 mm. per hour; May 15, 85 mm.; May 21, 40 mm.; May 27, 25 mm.; June 3, 14 mm.; June 10, 18 mm.)

CASE 4.—J. L., a 5-year-old Negro girl, was admitted to Metropolitan Hospital from the Cardiac Clinic on March 17, 1947, for a tonsillectomy. A diagnosis of rheumatic fever was first made in October, 1946, when, because of epistaxis and cardiac findings, she was hospitalized at Flower and Fifth Avenue Hospital for two months. The past history revealed little else besides an occasional sore throat.

On admission to Metropolitan Hospital the only positive findings were an enlarged heart with apical presystolic and systolic murmurs, and the large, obstructive, chronically diseased tonsils. The x-rays of the heart showed enlargement to the left and right. The sedimentation rate (Westergren) was 8 mm. per hour, white blood count 6,100 with 62 per cent polymorphonuclears and 38 per cent lymphocytes; hemoglobin 69 per cent. An uneventful tonsillectomy and adenotomy were performed on April 6. The child's condition remained unchanged until April 23, nine days after smallpox vaccination which had resulted in a typical primary vaccinia reaction. At this time there was evidence of reactivation of the rheumatic disease with a sedimentation rate of 50 mm. per hour. On April 28 the sedimentation rate had risen to 90 mm. On May 1 the temperature became elevated for the first time and rose to 104° F. that same evening: it remained at this high level for three more days. Nothing new was found on physical examination during this episode. The child then showed gradual improvement with a slow return of the sedimentation rate to normal and was discharged on June 16, 1947. (Sedimentation rates: May 7, 25 mm.; May 13, 80 mm.; May 15, 70 mm.; May 21, 30 mm.; May 26, 14 mm.; June 3, 14 mm.; June 10, 5 mm.)

CASE 5.—P. C., a 3½-year-old white boy, was admitted to Metropolitan Hospital on March 16, 1947, because of fever and pain in the legs and neck. His past history was negative except for measles at 2½ years of age. On admission the physical examination revealed a swollen, hot, tender right knee, a loud-blowing systolic murmur, and injected pharynx and tonsils. The temperature was 101° F. at this time.

X-ray showed a normal cardiac silhouette. Electrocardiogram demonstrated only left axis deviation. The Vollmer patch test was negative. The hemogram showed white blood cells 9,800, with 71 per cent polymorphonuclears and 29 per cent lymphocytes. The sedimentation rate (Westergren) was 115 mm. per hour.

Soon after hospitalization the patient began to improve. His temperature returned to normal within twenty-four hours, and the knee in about forty-eight hours. The sedimentation rate fell gradually (March 20, 80 mm. per hour; March 26, 40 mm.; April 8, 18 mm.; April 16, 10 mm.). On April 14, the patient was vaccinated and had a typical primary vaccinia reaction. On the fourth day following vaccination, the temperature suddenly rose to 102° F. and a purulent otitis media was found. The child was given 15,000 units of penicillin intramuscularly every three hours for one week (April 18 to April 25) followed by complete regression of the infection. The sedimentation rate on April 23, nine days after vaccination and five days after discovery of the otitis, had again become elevated (40 mm. per hour), but rapidly returned to normal (April 28, 10 mm.; May 7, 6 mm.; May 13, 6 mm.). On May 14, the child developed varicella and was transferred to Willard Parker Hospital.

CASE 6.—W. J., a 7-year-old Negro girl, was admitted to Metropolitan Hospital on April 8, 1947, because of right-lower-quadrant abdominal pain. The past history revealed frequent colds and sore throats, vague pains in the knees, shoulders, and elbows, and occasional epistaxis.

The abdominal pain complained of on admission had been present intermittently for one month. It had never been severe but recurred several times daily, each time persisting for less than an hour. There was no radiation and it was unaccompanied by nausea or vomiting. Physical examination on admission disclosed only an upper respiratory infection. The heart was apparently normal.

X-ray and electrocardiograms were normal. The Vollmer patch test was negative. The urinalysis was also negative. The hemogram showed a moderate anemia and a slight leucocytosis with shift to the left (red blood cells 3,500,000, hemoglobin 65 per cent, white blood count 13,900 with 73 per cent polymorphonuclears and 27 per cent lymphocytes). Sedimentation rate (Westergren) was 60 mm. per hour. A sickling test was negative.

The child was vaccinated on April 16, with a resulting typical primary vaccinia reaction. The temperature, which had always been below 100° F., rose above this level two days following vaccination and remained between 100° and 101° F. for one week before reverting to normal. The sedimentation rate, which had been returning to normal, also became elevated (April 16, 20 mm.; April 23, 40 mm.; May 9, 30 mm.). On May 14, the child developed varicella and was transferred to Willard Parker Hospital. No follow-up was obtained.

Five patients (Cases 7, 8, 9, 10, and 11) were known rheumatics ranging in age from 6 to 12 years; all of them were vaccinated during April, 1947. In all of these cases the vaccination took, but there were no undesirable side effects, and no reactivation of rheumatic fever occurred in these children.

COMMENT

The majority of workers in the field believe that reactivation of rheumatic fever most frequently follows upper respiratory infections. Prevention of this type of infection has been one of the goals in rheumatic fever control. The use of sulfonamides, antibiotics, or long sojourns in warm, dry climate, have all had this purpose in mind.

Unpredictability of rheumatic fever reactivation makes any evaluation of the role of antecedent events hazardous. The vaccination in the cases presented here had to be done during April, which is the season of high incidence of rheumatic fever, so that coincidence with other outside factors cannot be safely excluded. It is obvious that there may be many factors acting as a trigger mechanism for reactivation, but the reactivation following smallpox vaccination, in the described cases followed so similar a pattern, that there is a strong probability of it being the cause. Definite proof of this occurrence, however, could only be given if this phenomenon could be observed in a much larger series. It would have to be compared with the same number of rheumatic fever patients during the same season of the year, and under the same conditions, without vaccination. Only if the incidence of reactivation after vaccination were a much higher one than in cases not vaccinated, would the phenomenon be proved. Possibly in cases with undetectable subclinical activity and a disturbance of the antigen antibody balance, any trauma may lead to reactivation.

The presented cases indicate that vaccination can probably act in the same harmful manner as upper-respiratory infections. With the danger in mind, patients with rheumatic fever should only be vaccinated if directly exposed to smallpox.

Although the number of cases presented is small, the facts are striking. It is interesting to note that reactivation follows vaccination much earlier than upper-respiratory infections, usually on the first or second day after the take, a fact that cannot be explained at the present time. Just as it is known that reactivation does not always follow upper-respiratory infections, so reactivation

following smallpox vaccination was not seen in all of the present cases. It is difficult to explain the mechanism of recurrence of activity following vaccination.

Allergic manifestations such as purpura and urticaria frequently follow smallpox vaccination. Whether the reactivation of rheumatic fever is an allergic manifestation or whether it is a consequence of secondary infection at the site of the vaccination, should be a matter for future investigation.

SUMMARY

1. Six cases of reactivation of rheumatic fever following smallpox vaccination have been presented.

2. The possibility that this reactivation was due to the vaccination has been discussed.

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Case Reports

EDEMA ASSOCIATED WITH TEMPORARY IDIOPATHIC HYPOPROTEINEMIA

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INTRODUCTION

SINCE 1936 only two cases of idopathic edema in childhood have been reported in the literature. On the other hand several cases in adults have been reported. These cases have been grouped together under the heading of idiopathic edema not because they are necessarily related in etiology, but because in each instance the origin of the edema has not been determined.

Our report is that of an 8-week-old infant in whom the occurrence of a low-total serum protein is not related to any of the usual causative factors of hypoproteinemia. Concentrated salt-poor human serum albumin was made available to us‡ and, to our knowledge, this is the first report of its use in an infant with idiopathic hypoproteinemia.

CASE REPORT

J. C., an 8-week-old white male infant, was admitted to the Albany Hospital on Jan. 15, 1949, with the chief complaint of severe edema of six weeks' duration involving the entire lower half of the body, including the legs, genitals, and lower abdomen.

The infant was born after an uncomplicated, full-term pregnancy and delivery. Birth weight was 6 pounds, 12 ounces. The neonatal period was normal. The baby was fed an evaporated milk formula and vitamins. By the time of admission cereal had been added to his diet. His appetite was good, and at no time had there been any vomiting or diarrhea. The stools had always been normal in consistency and color. His weight at 5 weeks of age was 9 pounds, 8 ounces, a gain of 2 pounds, 12 ounces. During the three weeks preceding admission his weight increased 2 pounds, 4¾ ounces.

When the infant was about 2 weeks of age the mother noted that his scrotum was beginning to enlarge. By 6 weeks of age scrotal edema was very marked. Also at this time transitory swelling of the eyelids was noted when the infant cried. In addition, increase in the size of the legs, especially the left, occurred. The swelling increased progressively until, at the time of admission, the skin over the thighs was quite tense. The baby was more irritable than usual, but otherwise he showed no untoward symptoms.

Family history was noncontributory.

Physical Examination.—The infant appeared to be a well-developed, well-nourished white male weighing 11 pounds, 12¾ ounces and having a normal

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‡The serum albumin used in this study was processed by the American Red Cross from blood which it collected from voluntary donors. This is one of a series of investigations on serum albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value, a full report to the medical profession on the use of serum albumin in medical practice will be published.

temperature. He was irritable but was in no acute distress. The entire lower half of the body was greatly distended with pitting edema, especially the legs, genitals, and the lower abdomen. When the baby cried the periorbital regions became swollen.

Skin turgor was normal. There was severe excoriation of the perineum and genitals. Small cervical lymph nodes were present bilaterally, but no other lymphadenopathy was noted. The head was normally shaped. Marked craniotabes was found in the left occipital and left parietal regions. The eyes were normal except for the marked periorbital edema present when the baby cried. Ears, nose, and mouth were normal. The pharynx was slightly injected.

The neck was supple. The thorax was normal in shape. The lungs were clear to percussion and auscultation. The heart was normal in size to percussion, the sounds were of good quality, and there were no cardiac murmurs. The lower half of the abdomen was distended with marked subcutaneous edema. The baby was tense and voluntary spasm made palpation of the abdominal organs impossible. No fluid wave or shifting dullness could be defined. The penis, scrotum, and both legs were very edematous. Slight edema of the upper extremities, most marked in the hands, was present. The skin color in these areas was normal.

Laboratory Data.—The admission urine specimen was clear and yellow The specific gravity was not determined because of insufficient quantity of urine. The pH was 6.0. No albumin, sugar, acetone, or bile was found. Microscopic examination revealed no cells or crystals. The admission hemoglobin was 10 Gm.; red blood cells numbered 3.27 million; white blood cells 8,450 with 65 per cent polymorphonuclear cells, 25 per cent lymphocytes, 6 per cent monocytes, and 4 per cent eosinophils; blood platelets appeared to be normal in number. Subsequent blood counts did not vary appreciably from the admission count. The blood Wassermann and Kahn tests were negative. No reaction was produced by 0.1 c.c. of Old Tuberculin 1/1,000 intracutaneously. The McClure-Aldrich test revealed absorption of intradermal saline in five minutes. A chest x-ray revealed clear lung fields and a heart which was normal in size and contour. A flat film of the abdomen was normal. The results of further laboratory tests are given in Table I.

Hospital Course.—After the initial studies we were able to secure concentrated salt-poor human serum albumin and to observe its effect on our patient. Its use was divided into two periods. The first extended from the sixth to ninth hospital days with daily intravenous doses of 5, 10, 5, and 5 Gm. During this period the infant was kept on a Bradford frame and his intake, consisting of a Lonalac formula, and his output were analyzed for nitrogen. For these four days the total nitrogen intake, including the intravenous albumin, was 20.8 Gm., and the stool and urine excretion contained 4.35 Gm. of nitrogen. No albumin appeared in the urine, and the total serum protein rose from 2.1 to 2.4 Gm. per cent. No clinical improvement was noted during this first period and the weight fell only 3¼ ounces. However, during the five days following this first period there was a total weight loss of 17 ounces. Because of generalized tonic-clonic convulsions on the fourth, fifth, and sixth days of hospitalization, the infant was given 6 Gm. of calcium lactate orally each day and no further convulsions occurred.

The second period lasted from the fourteenth through the eighteenth hospital day, during which time 10 Gm. of concentrated salt-poor human serum albumin were given daily. Nitrogen studies of intake and output were not done. On the second day of this period there was 2-plus albumin in the urine; only a trace was found on the fifth or last day of the period; and no albumin was found on all subsequent days following this period of therapy. The total serum protein rose from 2.5 to 3.0 Gm. per cent. The baby became less edematous and the

weight fell 11 ounces. The hematocrit was 35 per cent on the first day and 34 per cent on the last day of the period. The red blood-cell count and hemoglobin remained unchanged. No blood-volume studies were carried out, but as judged by hematocrit and hemoglobin determinations there was no marked increase in plasma volume as is often seen in adults receiving concentrated salt-poor human serum albumin intravenously.[1] The results of these two periods are presented in Tables II and III.

TABLE I. RESULTS OF LABORATORY BLOOD TESTS

DATE	NPN (MG. %)	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)
Jan. 17	38	1.92	1.45	0.47
Jan. 20	—	2.10	—	—
Jan. 24	—	2.40	2.10	0.30
Jan. 28	38	2.50	2.40	0.10
Feb. 2	35	3.00	2.80	0.20
Feb. 5	40	3.10	2.50	0.60
Feb. 12	—	3.40	2.20	1.20
Feb. 19	35	2.80	1.90	0.90
Mar. 19	—	5.70	3.70	2.00
May 5	—	6.50	4.30	2.20

DATE	CALCIUM (GM. %)	PHOSPHORUS (MG. %)	SERUM SODIUM (MEQ./L)	SERUM POTASSIUM (MEQ./L)	SERUM CHLORIDE (MEQ./L)	CO_2 CONTENT (VOL. %)
Jan. 17	—	—	—	—	—	29
Jan. 20	6.4	—	130	5.1	103	—
Jan. 24	6.2	4.8	—	—	—	—
Jan. 28	7.4	—	—	—	—	—
Feb. 2	7.8	3.8	—	—	—	42
Feb. 4	—	—	144	6.0	110	—

Jan. 17	Blood sugar, fasting	62 mg. %
Jan. 17	Whole blood chlorides, as NaCl	576 mg. %
Jan. 20	Alkaline phosphatase	7.6 Bodansky U.
Jan. 26	Cholesterol, total	131 mg. %
Jan. 26	Cholesterol, free	53 mg. %
Jan. 27	Edema fluid, abdominal wall, total protein	306 mg. %
Feb. 4	Bromsulfalein test—4.4% of dye remaining after 45 minutes	

TABLE II. FIRST PERIOD

DAYS	1	2	3	4	5
IV Albumin Gm.	5	10	5	5	0
Total serum protein (Gm. %)	2.1	—	—	—	2.4

Weight loss—3¼ ounces
Total nitrogen intake for period (feedings + IV albumin)—20.8 Gm.
Total nitrogen output for period—4.35 Gm.

TABLE III. SECOND PERIOD

DAYS	1	2	3	4	5	6
IV Albumin (Gm.)	10	10	10	10	10	0
Total serum protein (Gm. %)	2.5	—	—	—	—	3.0
NPN (mg. %)	38	—	—	—	—	35
Hemoglobin (Gm. %)	12	—	—	10	—	11.5
R.B.C. million per mm.^{3}	3.5	—	—	3.2	—	3.5
Packed cell volume (%)	35	—	—	35	—	34
Urine albumin	0	2+	—	—	Trace	0

Weight loss—11 ounces

The infant was discharged on the twenty-second hospital day weighing 9 pounds, 13 ounces and having a total serum protein of 3.1 Gm. per cent. With the exception of the periorbital swelling, his edema had completely disappeared. He was to be followed by monthly weight checks and total protein determinations.

Subsequent to discharge the baby lost all traces of edema within six weeks, the periorobital edema being the last to disappear. The total serum protein rose and on May 5, 1949, three months after discharge from the hospital, it was 6.5 Gm. per cent with albumin 4.3 Gm. per cent and globulin 2.2 Gm. per cent. The infant has been in excellent health with the exception of severe bronchopneumonia in early April. In the latter part of May, 1949, his diet of Lonalac was changed to one of whole milk together with cereal, puréed fruits, and vegetables. On May 15, 1949, at 5 months of age, his weight was 15 pounds. In December, 1949, at the age of one year, he was well and was free of edema.

DISCUSSION

Shortly after admission it became evident that the baby's edema could not be accounted for by the usual causative factors. No evidence of circulatory insufficiency, hepatitis, nephritis, or nephrosis existed. Anemia was not marked for an infant of this age, and the protein intake had been adequate. There had been no excessive ingestion of sodium chloride and water. No allergic factors were noted. Although the infant's buttocks were severly excoriated upon admission, the edema had begun prior to the infection. Furthermore, the infection cleared within a few days after admission, whereas it was several months before the total serum protein was normal.

Having ruled out these usual causative factors, the problem of diagnosis resolved itself into a consideration of the more likely causes of hypoproteinemia in this patient. These may be grouped into three major categories: (1) Inadequate intake or absorption. The history and the finding of a positive nitrogen balance during the hospital stay suggest satisfactory consumption and absorption of protein. (2) Loss of protein from the body. In view of the history of normal stools this was not thought to be a causative factor. The absence of albumin in the urine, the absence of increased protein in the edema fluid, and the positive nitrogen balance during one of the hospital studies further ruled out this category. (3) Faulty protein formation resulting from an abnormality either in synthesis or in catabolism. A temporary defect in either the synthesis or the catabolism of the serum proteins as a cause of this infant's hypoproteinemia remains to be considered after exclusion of the other factors. An abnormality in protein catabolism is further supported by the fact that the intravenously administered concentrated human serum albumin raised the total serum protein level less than 1 Gm. per cent.

In the first of the two cases in childhood reported heretofore, Thompson, McQuarrie, and Bell[2] were able to relate the hypoproteinemia to an unusual atrophy of hepatic cells in the intermediate and peripheral areas of the liver lobules. Their case was one of a 2-year-old girl who had had edema and hypoproteinemia since the age of 13 months. She died following an attack of pneumonia and otitis, and the interesting liver pathology reported was found at necropsy.

A second case reported by Schick and Greenhaum[3] was that of a 12-year-old girl who had had recurrent edema since the age of one year associated with hypoproteinemia, especially of the globulin fraction. Electrophoretic analysis of her serum globulin revealed a very marked decrease of gamma globulin. They concluded that the hypoproteinemia was probably due to a congenital deficiency in the liver, bone marrow, or reticulo-endothelial system resulting in a defect in the synthesis of plasma proteins.

No clinical evidence of liver dysfunction was apparent in our case. A bromsulfalein test resulted in 4.4 per cent retention of the dye after forty-five minutes, a normal value. We feel that if our patient develops recurrent edema, a liver biopsy would be of great interest in view of the case reported by Thompson and associates.[2]

The total of 75 Gm. of concentrated salt-poor human serum albumin administered intravenously raised the total serum protein 0.9 Gm. per cent. In view of this small rise it is interesting to speculate on the possibility of further abnormalities in protein or amino acid metabolism in our infant. The fate of intravenously administered concentrated serum albumin in the body certainly warrants further investigation. After administering concentrated albumin it was six weeks before the clinical edema disappeared and three months before the total serum protein level was normal. These facts make it difficult to believe that its use had any appreciable effect on the course of this baby's hypoproteinemia. The absolute cause of his hypoproteinemia remains unknown.

CONCLUSION

A case falling into the general category of idiopathic edema associated with hypoproteinemia is presented. A brief survey of the literature including two previous cases in childhood is made. It is postulated that the hypoproteinemia in our case is the result of temporary abnormality in both protein synthesis and protein catabolism. The use of concentrated serum albumin in this case is discussed, and the need for further elucidation of its fate after intravenous administration is suggested.

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INGUINAL HERNIA IN A THREE-MONTH-OLD INFANT CONTAINING ADNEXA

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ON JAN. 24, 1949, a 3-month-old female child, S. R., was examined in consultation with Dr. A. H. London. The parents were both healthy and the child had been delivered normally at full term. At 2 months of age, the mother noticed a swelling on the right side of the pubis. The swelling seemed to be tender to palpation, and the mother thought it became larger when the child was crying.

Twenty-four hours before examination, the mass had increased in size, the child had cried considerably and had vomited once. Subsequent feedings and the stools were normal. The child was chubby, quiet, and well, except for the aforementioned swelling. This was a rounded, semisolid oval mass, $3 \times 0.5 \times 0.5$ cm., palpated at the upper portion of the labia on the right side. There was a thickened cordlike structure extending up into the inguinal canal. It could not be reduced.

A cyst of the canal of Nuck or an incarcerated inguinal hernia containing omentum or bowel were considered as diagnoses. It seemed unlikely that bowel could be incarcerated as the swelling was tense with no evidence of obstruction. The presence of omentum also seemed improbable as omentum is always very small in a child.

An operation was advised but the mother refused. She returned with the patient after eighteen hours because the swelling was larger and vomiting of a portion of several feedings had occurred.

On admission to Watts Hospital, the findings were the same as described above except that the mass was larger and more tense. The temperature and routine blood and urine studies were normal. An operation was again advised and performed within a few hours. An indirect inguinal hernia containing the right Fallopian tube, ovary, and the right half of the body of the uterus was found. The tube and ovary were edematous but not gangrenous, and they were returned to the abdominal cavity, the sac ligated and the hernia repaired. Fine cotton was used throughout. The recovery was uneventful, and the child discharged after four days. Re-examination five months later showed the hernia to be well healed.

DISCUSSION

A review of the literature for similar cases disclosed their rarity. Lapeyrie and Cabanac[1] reported two cases in 1934. In both patients the swelling was primarily in the labia majora. Also in both patients, the adnexa was excised. One contained only the ovary. Matassi[2] in 1940 reported a 2-month-old infant with both an umbilical and right inguinal hernia. The latter was irreducible and contained an ovary which was removed at operation.

The appearance of the adnexa in an inguinal hernia is unusual. The small bowel is present in 50 per cent of all cases. In order of frequency, the omentum follows, then the cecum, appendix, sigmoid, colon, bladder, ovary, tube, uterus, and last the stomach and liver. Watson[3] states that an irreducible hernia in a girl almost always contains the ovary. Early operation is advised as strangulation with subsequent sacrifice of the adnexa will ensue.

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AUREOMYCIN IN STAPHYLOCOCCEMIA, COMPLICATING AGRANULOCYTOSIS FOLLOWING TRIDIONE

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SINCE its release for general use about three years ago, trimethadione N N R (Tridione) (3,5,5-Trimethyloxazolidine-2,4-dione) has occasionally been reported as the cause of various severe skin reactions, aplastic anemia, and agranulocytosis. Harrison and Johnson[1] reported the first case of a patient with aplastic anemia in 1946, followed shortly by the report of MacKay and Gottstein.[2] Both of these patients died. There are four additional fatal cases reported to the present time.[4, 5, 6, 8] Van Wetzel[7] described a patient with a mild neutropenia and purpura, with an exfoliative dermatitis following use of Tridione.

The purpose of this paper is to present the case of a patient with severe agranulocytosis, hemolytic *Micrococcus aureus* septicemia, and a generalized exfoliative dermatitis, who recovered with use of aureomycin.

Sepsis usually is the complication which leads to fatality in patients with agranulocytosis. Hawkinson and Kerr[3] reported one such patient who had staphylococcemia, agranulocytosis, and severe anemia.

In reviewing the literature of the last fifteen years on granulocytopenia, it is interesting to correlate agranulocytosis with the therapeutic drugs in use at the time. Previous to 1937, the chief offenders were arsenic and its derivatives and aminopyrine and its derivatives. Between 1937 and 1943 these agents continued to be prominent, but in addition to them prontosil, sulfanilamide, and the early sulfa derivatives were used. Between 1943 and 1949, arsenicals and aminopyrine show up less frequently as offenders and sulfa derivatives are paramount. Added to these recently are the thiourea derivatives, and in the last three years, Tridione.

A list of agents reported to cause agranulocytosis includes arsenicals, aminopyrines, sulfonamide drugs, benzene, thioureas, gold, Atabrine, cinchophen, pyrithyldione, Tridione, and occasionally barbiturates.

When Tridione was first tried clinically, skin rashes and blurring of vision in bright light were reported, with occasional nausea and drowsiness.

CASE REPORT

History.—C. L., a Negro boy 12 years of age, was born full term and had had a spontaneous delivery with no neonatal difficulties. His growth and development were considered normal. The history indicated a questionably adequate vitamin intake, and the child had received no routine medical care. He had had the usual childhood diseases without serious sequelae. The family history revealed that the father had had "a fit or two" when the boy was 12 months old.

At 4 years of age, the patient began having clonic seizures, generalized, with no known exciting cause. These attacks increased in frequency and intensity, occurring two or four times a day and lasting up to ten minutes. The patient was also having from three to four petit mal attacks a day.

Eighteen months before admission he was given dilantin sodium, 0.4 Gm. per day, by his family physician, with no obvious change in either type of seizure noted by the parents. He was then referred to the Duke Hospital Pediatric Clinic, where he was seen to have generalized clonic seizures, starting in the arms, lasting from thirty to forty-five seconds, during which there was no lapse

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of consciousness. Physical and neurological examinations were otherwise negative, routine laboratory data were normal, and a serologic test for syphilis was negative. An electroencephalogram showed a generalized and paroxysmal cerebral dysrhythmia, with bursts and runs of spike and wave, and atypical spike and wave activity. It was interpreted as showing grand mal, petit mal, and larval petit mal patterns. He was sent home on phenobarbital 30 mg., three times a day, dilantin sodium 0.3 Gm. four times a day, and a diet high in butter and fried foods. Excess fluids were prohibited, the total intake being limited to 100 c.c. per day.

One week later the major seizures were well controlled, but the minor attacks continued. For this reason, Tridione, 0.3 Gm. three times a day, was added. This date was six weeks before his admission to the ward.

After one month of Tridione therapy, the minor attacks were limited to one a day and the major attacks occurred about once a week. On this visit the patient was noted to have had a cold and cough for one week and fever for four days. He had received two doses of a sulfonamide preparation four days previously. A chest x-ray was negative, hemoglobin 14 Gm., white blood count 14,200. The patient was given 300,000 units of procaine penicillin, and continued on the same anticonvulsive medication.

TABLE I. BONE MARROW VALUES ON THIRD AND SIXTEENTH HOSPITAL DAYS

CELLS	THIRD HOSPITAL DAY	SIXTEENTH HOSPITAL DAY
Polymorphonuclears segmented	0	16
Polymorphonuclears, nonsegmented	0	27
Metamyelocytes	10	15
Neutrophil myelocytes	3	7
Promyelocytes	15	8
Myeloblasts	7	0
Eosinophils	0	0
Basophils	1	1
Small lymphocytes	7	4
Large lymphocytes	0	0
Lymphoblasts	0	0
Reticulum cells	2	0
Hemohistiocytes	0	0
Plasma cells	0	0
Megaloblasts	0	0
Erythroblasts	20	1
Normoblasts	36	22

Three days following the above visit, the boy's parents began to notice a dry peeling of the skin, which soon became generalized, and he also showed an edema of the face plus cough, sneezing, and rhinorrhea. Seven days later he was seen in the convulsive clinic and his hemoglobin at this time was 14.5 Gm., and leucocyte count 11,300. An intradermal skin test was done with dilute penicillin and observed at fifteen- and 30-minute intervals. The test was reported as "negative." He was continued on dilantin and Tridione, and given penicillin tablets, 40,000 units every six hours for the apparent respiratory infection.

One week later he was seen with fever of 40.6° C., extreme weakness, cough productive of a mucoid sputum, and continued peeling of the skin. He was admitted for treatment. Physical examination revealed a dry, scaly, uninfected, generalized exfoliation of the skin, crackling râles in the chest anteriorly and posteriorly, with long expiratory wheezes. The pulse was rapid and the heart had a poor quality first mitral sound, the blood pressure was 120/60-40. There was 2-plus pitting edema of both feet.

Laboratory Findings.—Laboratory findings showed a 2.24 million red blood count, a 5.5 Gm. hemoglobin, and a 2,560 leucocyte count with a complete absence of granulocytes. The reticulocyte count was 8 per cent and there were 10 normoblasts per 100 white blood cells. Platelets were normal in number. The stool and urine examinations were negative, as was the serologic test for syphilis. A throat culture revealed a nonhemolytic Streptococcus, *Escherichia coli*, and *Aerobacter aerogenes*. The admission blood culture, reported on the third hospital day, showed a hemolytic *M. aureus*, diffuse in all cultures. The blood bilirubin was normal. Urinary urobilinogen done on the fourth day showed 0.13 Ehrlich units in two hours.

On the third hospital day a bone marrow aspiration biopsy was done. The marrow was definitely hypocellular with the predominant cells being early promyelocytes containing abnormal granulation, and immature erythroblasts. Megakaryocytes were present.

On the sixteenth hospital day, a repeat study of the marrow showed normal cellularity, a marked increase in mature granulocytes, with a compensatory maturation acceleration. (Table I.)

Course.—The patient was immediately started on aureomycin, 2 Gm. per day in eight divided doses, and all anticonvulsive drugs were discontinued.

COURSE OF TEMPERATURE, CULTURES, LEUCOCYTES, % GRANULOCYTES, AND HEMOGLOBIN

	HOSPITAL DAYS																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
RECTAL TEMPERATURES DEGREES CENTIGRADE (41°, 40°, 39°, 38°, 37°)																						
AUREOMYCIN DOSAGE	AUREOMYCIN — 2 GRAMS																					
BLOOD CULTURES		+	0	0	+	0		0	0	0	0		0		0		0	0	0	0	0	0
TOTAL LEUCOCYTE COUNT (in thousands)	2.5	1.8	2.4	3.9	4.3	7.9	16.0	12.2	14.1	14.0	12.3	7.7		7.4	5.6	4.6		4.7			4.1	5.9
% GRANULOCYTES	0%	0%			67%		88%							49%							66%	
HEMOGLOBIN GRAMS	5.5	5.7				11.5	11.2				11.5				11.5						11.0	
TRANSFUSION			500 cc.																			

Chart 1.

The response was dramatic. Within thirty-six hours the patient's condition was subjectively improved, and at the end of seventy-eight hours on aureomycin his temperature became normal and remained so. A transfusion of 500 c.c. of whole blood was given without reaction. Corresponding to the fall in temperature was a rise in leucocytes, so that on the fourth day of normal temperature, the leucocyte count was 16,000, with 88 per cent granulocytes (see Chart 1). Blood platelets were normal throughout, and there was no hemorrhagic tendency. A second positive blood culture was obtained on the fifth hospital day for hemolytic *M. aureus*, even though on this day the temperature was normal.

Following this abrupt improvement the patient's course was uneventful. Aureomycin was continued two weeks after the last positive blood culture was obtained. Convulsive seizures, which had been entirely absent during the above illness, recurred after three weeks and were controlled eventually on Mesantoin. The patient was to be followed in the convulsive and pediatric clinic.

DISCUSSION

This patient is interesting from many aspects. First, he reemphasizes the fact that patients treated with Tridione should be closely followed and, at the earliest signs of intolerance, the drug should be stopped. These signs may occur from twelve days up to ten months after therapy has started.

Staphylococcemia is a little publicized complication of agranulocytosis, although it frequently occurs in other conditions. The hemolytic *M. aureus* found in this patient was subjected to penicillin sensitivity tests, and it was found to be not inhibited by penicillin in concentrations of 100 Oxford units per c.c. This is quite in accord with the findings of Nichols and Needham,[9] who found that twelve out of fifteen strains of this organism isolated from a bacteremia were insensitive to penicillin. Sensitivity tests to aureomycin showed inhibition at eight hours to 6.25 micrograms of aureomycin. These tests were done after a clinical trial of aureomycin had already demonstrated that the organism responded well, and confirmed the fact that aureomycin was the drug of choice in this patient. Penicillin was not used as it can cause exfoliative dermatitis, although in Van Wetzel's patient, this appeared on the twelfth day of therapy with Tridione. In the presence of a total granulocytopenia, some antibiotic was direly needed, and one which had not been reported to cause suppression of leucocytes was selected. Also, physical findings in the lung fields seemed to represent the atypical type of pneumonitis in which aureomycin has proved to be very effective. By the time the staphylococcemia was reported, the patient had begun to show marked improvement, and the medication was continued.

In retrospect, it seems likely that the skin reaction, the rhinorrhea, the cough with asthmatic wheezes, and possibly the low-grade fever seen with the "cold" preceding the patient's admission all could have been drug sensitivity manifestations. Certainly this set of symptoms in the presence of sulfa therapy has been described repeatedly, and the appearance of cutaneous changes during chemotherapy has long been regarded as an ominous sign. Shaffer and Morris[10] report a case of severe erythema multiforme of the pluriorificial type (Stevens-Johnson syndrome) resulting in blindness in a patient after two weeks of treatment with Tridione. In this patient there was also "wheezing, expiratory râles anteriorly, and large rhonchi were detected posteriorly."

The finding of an hypocellular marrow, with maturation arrest in the myeloid and erythroid series, and with toxic granulation present in the myelocytes, is a picture quite in keeping with suppression of the marrow due to a drug sensitivity reaction.

SUMMARY

1. A case of agranulocytosis, anemia, and exfoliative dermatitis with staphylococcemia following five weeks of Tridione is presented.

2. The response to treatment with withdrawal of the drug and the administration of aureomycin was prompt and dramatic.

3. Weekly examinations of the blood cells and platelets should be made early in therapy with tridione, and examinations at bimonthly intervals should be made throughout the course of therapy.

4. Appearance of cutaneous changes may be the earliest sign of drug toxicity, and asthmatic wheezes with rhinorrhea and fever may be present. Tridione should be stopped immediately in the presence of any of these findings.

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ACCIDENTAL ACUTE DILANTIN POISONING

Report of a Case With Complete Recovery in a Nonepileptic Child

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PHENYTOIN sodium (Dilantin) is a synthetic anticonvulsant drug with little hypnotic effect now widely used in the treatment of idiopathic convulsive disorders.

DOSAGE

Phenytoin sodium is supplied in 0.1 Gm. capsules; the average adult dose is 0.1 Gm. three or four times daily. It is recommended that children over 4 years of age be started on 0.1 Gm. daily and subsequent dosage be adjusted in accord with therapeutic response.

PHARMACODYNAMICS

Though phenytoin sodium is analagous in structure to the barbiturates, its chemical formula 5,5-diphenylhydantoin designates it as a derivative of glycol urea rather than malonyl urea. In studying the metabolism of this compound Hine and Kozelka[1] determined that the drug, because of slow destruction, tends to accumulate in brain tissue. Such storage, however, is not rapid, and thus toxic manifestations, when they occur, usually develop during a period of prolonged administration. In pharmacologic experiments in animals it has been shown that large doses of the drug produce a fall in blood pressure as well as a respiratory depression, while intravenously administered lethal doses result in respiratory death.[2] The mechanism by which phenytoin sodium prevents convulsive seizures in man is not known; its action has been shown to be highly selective for the motor cortex, however. Although rapidly absorbed from the intestinal tract, the maximum quantity of the drug which can be detoxified in a twenty-four-hour period in the adult is 0.6 Gm.[3, 4]

TOXICOLOGY

The prominent symptoms of acute Dilantin intoxication may be divided into two stages.[4, 5] Minor toxic reactions include dizziness, ataxia, tremors, blurred vision with diplopia and mydriasis, and slight nausea. More severe toxicity is manifest as vomiting and diarrhea, fatigue, irritabilty or apathy, difficulty in breathing or swallowing, nervousness, mental confusion, and occasionally as active hallucinations. Toxic reactions such as dermatitis and purpura, or hyperplasia of the gums are described in patients who have taken the drug regularly for more protracted periods.

CASES OF ACUTE INTOXICATION

Since the introduction of Dilantin by Merritt and Palmer in 1938 there have been only three reports in the literature describing acute intoxication in epileptic patients from ingestion of the drug. In 1940 Robinson[6] reported a case with recovery in a 25-year-old epileptic man who had attempted suicide by ingesting 45 capsules (4.5 Gm.) of the drug. Within thirty minutes the patient became drowsy and developed generalized tremors of the extremities; in another ten minutes he had lost consciousness. When seen at the hospital one hour following his attempted suicide, his skin was cold and damp, and his

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jaws were locked together. Within two hours after initiation of therapy, which included gavage and parenteral administration of stimulants, the patient was conscious and oriented. His only sequelae were urinary tract irritability and, for a few days, urethritis.

Aring and Rosenbaum[7] have described toxic effects from ingestion of large amounts of Dilantin in a 19-year-old epileptic patient who had been accustomed to taking the drug in "spree" fashion in successful attempts to derive exhilaration closely simulating acute alcoholism. On three separate occasions the patient had ingested 40 capsules (4 Gm.), 60 capsules (6 Gm.), and 70 capsules (7. Gm.). The patient's appearance on adminission to the hospital was that of a drunken man with reeling gait, thickened and rapid speech, generalized tremors of body musculature, and moderate nausea. Physical examination on each occasion disclosed blurring of vision and diplopia, dizziness and severe ataxia, and horizontal nystagmus; there was also a generalized hyperreflexia. Within three days following each of these episodes all symptoms had completely disappeared. At no time did the patient show involvement of the gums or buccal mucosa, and never was there any sedative or soporific effect. Later studies disclosed only a moderate leucocytic stimulation. The authors concluded that "large doses of Dilantin bring out signs usually associated with specific pyramidal tract involvement." This would indicate that "large doses of Dilantin cause no more severe symptoms than an alcoholic bout."

In 1947 a group of French physicians[8] reported a case of acute poisoning in a 42-year-old epileptic farmer who had ingested 44 capsules (4.4 Gm.) of Dilantin with suicidal intent. On admission to the hospital he presented a picture of generalized tremors, mental confusion, and eye signs of diplopia and nystagmus, together with slurring of speech and hyperactive reflexes. The authors regard the unusual findings of gum hyperplasia, inflammation, and hemorrhage as complicating this patient's acute symptomatology; however, in view of the failure of remission of the mucosal changes one week after all other symptoms had regressed, and inasmuch as similar findings are not described in connection with acute poisoning by other writers, they would seem rather a manifestation of chronic reaction to the drug which has been estimated to occur in about 15 per cent of epileptic patients who take the drug regularly in therapeutic dosage.[9]

CASE REPORT

About 10 A.M. of the day in question, A. N., a 4½-year-old white boy, swallowed 6 capsules (0.6 Gm.) of Dilantin Sodium which had been prescribed for his aunt's epileptic seizures. On advice of a local physician a cup of coffee was given as an antidote. At 2 P.M. that afternoon the parents noted that the child was walking unsteadily with staggering gait, and by 3 P.M. the child had developed such extreme weakness of neck musculature that he was unable to control the movement of his head.

The boy's mother stated that en route to the hospital the child had been exceedingly nervous and restless, and had complained of not being able to see clearly, stating that "everything looks blurry." While being examined, he had hallucinations that he was feeding lettuce to his pet rabbits and motioned as if to stroke the animals.

Physical examination in the Emergency Room of the Children's Hospital of Pittsburgh at 5 P.M. revealed a confused, pale child with marked tremors of his extremities, who was unable to express himself coherently. Attempts to stand and walk exaggerated the tremors so greatly that the boy could not maintain his balance. When lying in supine position he had definite weakness of the neck muscles and was barely able to rotate his head. It was impossible for him to

raise his head off the examining table. The patient's pupils were slightly dilated but reacted normally to light and accommodation. His reflexes were hypoactive but not otherwise abnormal. His skin was cool, his pulse was of small volume but with a regular rate of 84. His chest was clear and his abdomen quite soft. The rectal temperature at this time was 98.4° F. The patient was admitted to the service of Dr. Robert R. Macdonald.

Blood and urine studies performed at the time of admission were normal.

Within twenty minutes following admission, despite the hypodermic injection of an ampule (7½ grains) of caffeine sodium benzoate, the child's condition became more serious. His pulse rate increased to 128 and his blood pressure fell to 90/50. Moreover the patient's skin was cold and damp, his pupils appeared widely dilated and reacted only slightly to light, and his respirations were shallow and irregular. The child lapsed into a stupor, and when aroused his speech was thick and garbled; he did not recognize his parents.

At 5:45 P.M. normal saline solution was begun by slow intravenous drip and a second ampule of caffeine sodium benzoate was administered hypodermically. Although the patient experienced some difficulty in deglutition, he was persuaded to swallow one ounce of a saturated solution of magnesium sulfate.

At 6 P.M. the hypodermic was repeated; at 6:45 P.M. the child vomited 250 c.c. of thick yellow fluid containing numerous small strands of mucus.

At 7 P.M. after the patient voluntarily voided 210 c.c. of normal urine, 500 c.c. of 10 per cent glucose in water was added to the solution for intravenous infusion. At 7:15 P.M. the pulse rate fell suddenly to 100 and the blood pressure was 80/50; respirations were shallow and rapid, and the rectal temperature was recorded as 97.2° F. The patient was packed in hot water bottles and a fourth ampule of caffeine sodium benzoate was given; another hypodermic was given in half an hour. The child remained in a restless stupor and did not seem to rally well; accordingly, an ampule (20 mg.) of Benzedrine Sulfate was given slowly by vein. Shortly thereafter the patient roused, complained of nausea, and vomited several times.

By 8 P.M. the child was fully awake and oriented, but continued to complain of "seeing double." The tremors of his hands and legs seemed more marked, so that his extremities were in almost constant motion. The parents were instructed to keep the patient awake by conversing with him; about midnight, when the child's color had improved and his pulse and respirations were normal, it was believed safe to allow him to sleep. His rectal temperature at this time had risen to 98.6° F.

The patient continued to vomit small amounts of yellow fluid at frequent intervals throughout the night. At times he cried out in his sleep and was extremely restless; the tremors of his limbs gradually subsided.

By 8:00 of the morning following the child's admission he had regained full control of the motor power of his neck muscles, and physical examination at this time was entirely normal. Shortly after breakfast he fell into a deep, restful sleep interrupted only briefly during the next twenty-four hours for purposes of feeding and urination.

Laboratory studies performed on the second hospital day were normal except for a blood count which showed a mild polymorphonuclear leucocytosis of 11,400 cells.

On awakening on the morning of his third hospital day the patient seemed fully recovered and accordingly was discharged from the hospital.

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Addendum to Case Report of Congenital Toxoplasmosis

In 1948, a case was reported[1] having all the clinical characteristics of congenital toxoplasmosis, but the neutralizing antibody test was negative. At that time it was felt that despite the latter, this could be classified under toxoplasmosis.

However, recently more reliable tests as described by Sabin and Feldman[2] were performed on the bloods of the mother and child and reported as negative.

In view of that, it was felt[3] that it would be better to reclassify the above patient as a case simulating toxoplasmosis, but probably secondary to cerebral agenesia on a congenital basis.

JOSEPH SCHWARTZMAN

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CRETINISM AND MONGOLISM IN THE SAME FAMILY

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THE general similarity of cretinism and mongolism is apparent. Ruhräh described a painting in The Boston Museum of Fine Arts in which the infant shows some of the characteristics of mongolism and some of the characteristics of cretinism [a madonna and child by Montegna (1431-1506)].

The purpose of this paper is to report a case of cretinism followed by a mongoloid in the same family. A review of the literature for the past twenty years yielded one similar occurrence, reported by Collier in 1930. In a personal communication Benda stated that he knows of none reported, but recalled a similar situation occurring several years ago which was not reported.

The etiology of mongolism remains obscure. Benda states, "Potentially, mongolism can be the outcome of any pregnancy, if a constellation of factors occurs which produces a threshold condition of sterility." Ingalls states that mongolism is determined at about the eighth week of gestation. Quoting from his paper: "while the causative agents of mongolism are relatively numerous, the causative mechanisms are few in number and operate at about the eighth week." The etiology of sporadic cretinism is unknown.

CASE REPORT

Maternal History.—The mother is a 32-year-old college graduate. Her health has always been excellent except for the usual childhood diseases. Her menses began at 10 years of age. They have always been normal. There have been no miscarriages or abortions.

Three pregnancies have occurred. The first, in 1942, resulted in a normal female infant. This child is now 8½ years old and normal in every respect. Following the birth of the first child the mother was placed on thyroid extract by an army physician because of being tired. Thyroid of unknown dosage was taken for one month.

Two months ago, because of constant tiredness, she consulted her family physician. A summary of his findings showed hypotension, anemia, and a basal metabolic rate of minus 20. She has been on gradually increasing doses of thyroid extract since. In retrospect, the mother states she has been sluggish much of the time since her first pregnancy.

Cretinism.—The second child, born in 1947 (now 3 years old), was first seen at the age of 6 months for routine physical examination and immunization. She presented obvious signs of cretinism; however, the parents were not aware of any deviation from normal. The pregnancy had been uneventful. There had been no bleeding. The mother took a multi-vitamin preparation and liver concentrate with iron by mouth for several months. Blood pressure and urine were normal throughout. Delivery was spontaneous and the child cried immediately.

Developmental history was difficult to elicit because of the failure of the parents to observe any abnormality. Constipation had been a minor problem, occasionally requiring milk of magnesia. The child smiled at 3 months of age; she had always been considered a good baby. The baby had made no effort to turn, pull herself up, and could not sit up.

Examination revealed the following pertinent facts: hypotonia, apathy, pallor, and coarse black hair; weight 7,600 grams (16 pounds, 12 ounces), height 94.5 cm. (24 inches); anterior fontanel widely open, measuring 4 × 3.5 cm.

Blood studies showed a hemoglobin of 8.0 Gm. and a red cell count of 2,430,000. Blood cholesterol measured 415 mg. per 100 c.c. X-rays of the left wrist showed no ossification centers. Heart films and electrocardiogram studies were not done.

The child has been on thyroid extract for the past two and one-half years, beginning with a dose of 0.5 grain daily and increasing gradually to a dose of 1.5 grains at one year of age. The dose of thyroid has since been increased as tolerated and the child is now taking 2.5 grains daily. Her blood count has returned to normal. Serial wrist films every six months show slowly developing ossification centers with a present bone age of a slow 3-year-old. She is now normal in height and weight for her age. She talks considerably and is very active. Psychometric studies have not been done, but she closely approximates a 3-year-old child in her general developmental growth.

Mongolism.—The third pregnancy, like the others, was entirely normal. Delivery was uneventful and the child cried immediately. At birth the child was obviously a Mongolian idiot. The head was brachycephalic. The eyes were slanted and typical epicanthic folds were present. Hyperextension and hypotonia were marked and the hands were typical. This infant is now 18 months old and has shown consistent development of a Mongolian child. He recently has been institutionalized.

COMMENT

Many factors are considered to play a role in causing mongolism. Jenkins concluded that mongolism "is due to diminished viability of the ova." He cites as evidence the following facts: first, the incidence of mongolism increases with advancing age; second, the occurrence of mongolism in one of a pair of dizygotic twins; third, twins arising from a single ova are both affected. Cases of mongolism in both twins of different sexes are unknown.

Benda, in his theory of "threshold condition of hormonal sterility," offers the following evidence: first, physiological aging of the maternal organism for those beyond 41 years; second, for the age group 31 to 40, slow fertilization time, increased incidence of threatened abortion, high incidence of menstrual irregularities, and a high incidence of thyroid disorders. In his series 38.5 per cent of those between 31 and 40 years of age showed thyroid dysfunction.

The occurrence in the same family of cretinism and mongolism would suggest a common denominator. The added evidence of thyroid deficiency in this mother suggests a hormonal factor in the development of these two abnormal siblings. Benda, in his letter says, "The idea has occurred to me that if the thyroid deficiency, as a part of the picture, occurs especially in the second month, the result may be mongolism; but if the thyroid deficiency is not making itself manifest in the mother before a later part of the pregnancy, the result can be cretinism in the child."

Certainly evidence is accumulating which suggests that studies of the ovaries and endocrine status of the mother of Mongolian children would be of great value.

SUMMARY

A case of cretinism followed by a case of mongolism in the same family is presented. One previous similar family has been found. The mother of the two children reported here suffers from thyroid deficiency.

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Medical Progress

THORACIC SURGERY IN PEDIATRICS

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THE recent advances in surgical technique, anesthesia, chemotherapy, better understanding of cardiorespiratory physiology, and fluid balance have made it possible for the various thoracic surgical procedures to be carried out with a safety factor comparable to any of the major surgical operations; in no other field have the achievements been so dramatic as in pediatric thoracic surgery.

At the present time there is an almost endless list of surgical procedures for the correction and treatment of diseases of the chest in children; this paper, however, is primarily concerned with presenting the more common conditions encountered in the private practice of thoracic surgery.

GENERALIZATIONS

While in outward appearance a child may seem to be a small adult, he most certainly is not. The child's reparative processes predominate and the recuperative powers are much greater than in the adult. Probably the major cause of mortality in pediatric surgery is due to inadequate and ill-advised preparation of the patient.[1] The child must be carefully and adequately prepared for any thoracic surgical procedure.

Preoperative Preparation.—In addition to the usual routine history, physical examination, and diagnostic procedures, the confidence of the child should be gained if possible and full understanding should be made with the parents. The child must be evaluated clinically. Any anemia or dehydration must be corrected before surgery. Preoperative chemotherapy should be started.

Anesthesia.—The success of the operation to a large extent depends on the skill of the anesthetist. Well-timed and accurate preoperative medication is important. Ether continues to be the anesthesia of choice in children and should be administered through an endotracheal tube using a positive pressure technique.

Surgery.—The operation should be performed fairly rapidly, but not at the expense of careful handling of tissues, hemostasis, and meticulous dissection. During surgery, blood loss should be periodically evaluated and replaced in like amounts.

Postoperative.—Chemotherapy should be maintained as long as needed. Adequate fluid balance, including amino acids, plasma, blood, vitamins, and electrolytes, should be maintained. The active moving around of children, as compared with adults, will produce a decreased morbidity rate in general; but, due to lack of cooperation, more frequent tracheal aspirations and therapeutic bronchoscopies may be necessary to prevent and treat any occurrence of pulmonary atelectasis.

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ESOPHAGUS

Benign Obstruction.—By far the commonest cause of esophageal obstruction in children is cicatricial stenosis following a chemical burn. Obviously the best form of treatment is prevention. However, many patients are encountered following the swallowing of various corrosive chemicals, most notably lye, and when recovery occurs, a troublesome stenosis of the esophagus invariably results (Fig. 1).

Fig. 1.—Barium swallow demonstrating upper esophageal stricture due to the swallowing of lye.

Today as in the past, bougienage is the treatment of choice if adequate, but in a variable number of patients it will be extremely hazardous, impossible, or become distasteful to the point of intolerability over a period of time. Certain procedures developed in treating carcinoma of the esophagus are now refined to the point of safety that they may be used for treating benign obstructions. Resection and direct anastomosis would appear to be the procedure of choice.

Experimentally it has been demonstrated that the blood supply to the esophagus is adequate enough to allow mobilization, resection, and end-to-end anastomosis.[2] Tuttle and Day[3] reported six patients with short esophageal strictures treated in such a manner. Sweet[4] reported a case of high stricture of the esophagus treated by esophagogastrostomy. Several others have reported cases in which a segment of jejunem is used to replace the esophagus.[5, 6, 7]

Congenital Atresia and Tracheoesophageal Fistula.—This anomaly, while not common, has received considerable attention since the first successful direct anastomosis by Haight[8] in 1941.

The anomaly appears in several forms and is classified under five main types by Ladd[9]:

Class 1: The upper esophageal segment terminates in a blind pouch in the upper third and the lower segment is represented by a similar pouch, there being no communication with the trachea.

Class 2: The upper esophageal segment communicates with the trachea and the lower segment is a blind pouch.

Class 3: The upper segment terminates blindly and the lower segment communicates with the trachea above the carina.

Class 4: This is similar to Class 3 except that the lower segment communicates with the trachea at the carina or with the left or right mainstem bronchus.

Class 5: Both segments communicate with the trachea.

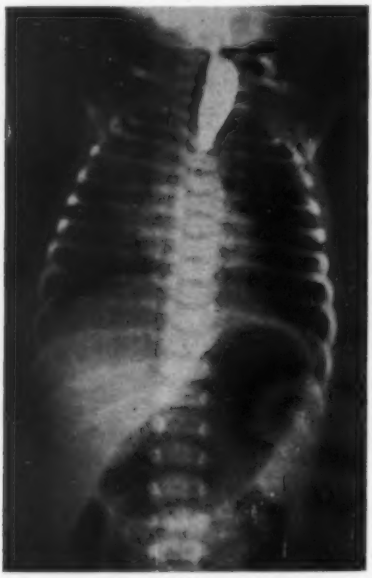


Fig. 2.—Tracheoesophageal fistula in a newborn infant. Upper blind pouch demonstrated with iodized oil; air in stomach indicates that the distal segment communicates with either the trachea or bronchi.

In a review of 84 cases,[10] 86 per cent were found to represent Classes 3 and 4 (Fig. 2).

The diagnosis is suggested by increased oral secretions, cyanosis, and regurgitation of feedings. Confirmation is obtained by x-ray studies using iodized oil to outline the upper segment with or without its tracheal communication.

Pulmonary complications have been a limiting factor in the surgical correction of this anomoly. Because of the danger of spilling over into the tracheobronchial tree, operation should not be postponed beyond the time necessary to prepare the patient for surgery. Haight[8] has recently reported 52 cases of patients subjected to surgery. In 40, the esophageal anastomosis was completed, and of these, 22 died and 18 recovered. Ladd and Swenson[11] reported

their experience with this anomaly. Thirty-nine primary anastomoses were carried out with 20 recoveries; 43 multiple stage procedures produced 16 living patients, of whom 5 subsequently had an antethoracic esophagus completed.

In view of the fact the anomaly is incompatible with life if untreated, these results represent a very high salvage rate.

DIAPHRAGMATIC HERNIA

Under this heading is listed any condition where the abdominal contents protrude into the thorax through an abnormal opening in the diaphragm (Fig. 3).

In an extensive review of personal cases, Harrington[12] lists the types of hernia in their order of frequency as: esophageal hiatus hernia, hernia of indirect

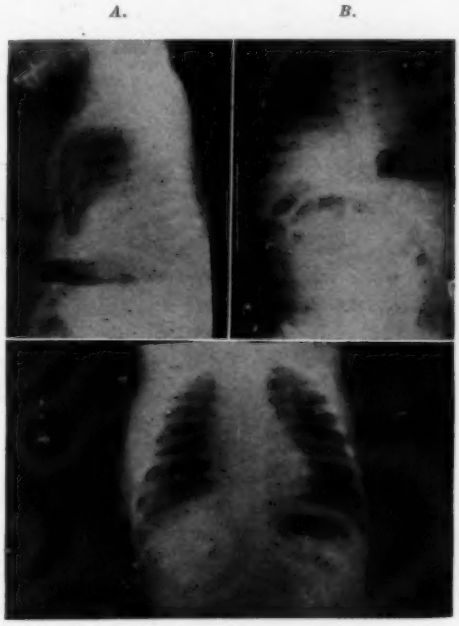


Fig. 3.—Diaphragmatic hernia in an infant; preoperative views, above, demonstrate eventration of diaphragm with liver and abdominal contents being present in the right side of the chest. Lower view is postoperative demonstration of results following surgical repair.

and direct trauma, congenital absence of a portion of the diaphragm, pleuroperitoneal hiatus, and subcostosternal hernia. He also offers a classification of diaphragmatic hernia which is both simple and logical:

1. Nontraumatic diaphragmatic hernia
   a. Congenital: Due to an embryonic deficiency; this hernia usually has no sac.
   b. Acquired.
2. Traumatic
   a. Direct and indirect injury.
   b. Inflammatory necrosis.

The symptoms are complex and depend on the amount of mechanical interference with the function of the herniated abdominal viscera, impairment of diaphragmatic function, and the amount of increased pressure in the thorax which impairs respiration and circulation.

The only type of treatment to relieve the condition is surgical repair. Whether the repair is made through the abdomen or transthoracically depends somewhat on the individual surgeon. However, Soutter,[13] in reviewing all the cases of surgical repair of hiatus hernia done at the Massachusetts General Hospital has concluded that the incidence of recurrence is lower and symptomatic relief greater after transthoracic rather than subdiaphragmatic repair.

MEDIASTINAL TUMORS

From an extensive review of the literature,[14] it is apparent that these tumors are relatively infrequent. Usually they are quiet lesions for a long period of time and only diagnosed by routine chest x-rays or after they begin producing symptoms due to their size and location. The most common primary types are those of the thymus and those arising from lymphatic tissue, dermoids and teratomas, and neurogenic tumors. Bronchogenic cysts, fibromas, lipomas, and intrathoracic goiters occur somewhat less frequently than the above, while other tumors are exceedingly rare.

The majority of tumors are malignant and many of the benign ones are potentially malignant. The majority are those originating in lymphatic tissue and secondary malignant tumors are not as yet amenable to surgery.

The symptoms are quite varied due to the various types of tumors, their size, and their location. The presence of these types of tumors is demonstrated by x-ray examination. The true pathology can often be diagnosed preoperatively, but usually an exploration with biopsy is necessary to make a correct diagnosis.

Unless there is a definite contraindication to surgery, all cases of mediastinal tumor should have an exploratory thoracotomy with the idea of complete excision, since the true cell type often cannot be determined in any other manner, and because excision, if complete, offers the best and often the only chance of a cure (Fig. 4).

CYSTIC DISEASE OF THE LUNG

With an increased use of the routine chest x-ray examination, cystic disease of the lung is now being recognized as a relatively common disease.

Much of the literature is concerned with the origin of these cysts. It is agreed that they may be either congenital or acquired and the true origin really makes very little difference except for academic interest. Given a specific case of cystic disease, it is impossible to definitely say whether its origin was congenital or acquired.[15]

The symptoms are classified as follows: 1. asymptomatic, 2. symptoms caused by increased pressure within the cysts, 3. symptoms caused by infection of the cysts, 4. hemoptysis, and 5. rupture of the cyst wall, resulting in simple or tension pneumothorax. Most patients with pulmonary cysts are asymptomatic, and only some complicating factor draws attention to their presence.[16]

The diagnosis is usually quite easy: the means of diagnosis being made by x-ray, bronchography, bronchoscopy, and biopsy. Occasionally the cysts may be confused with a neoplasm, lung abscess, tuberculous cavities, empyema, and spontaneous pneumothorax. However, as pointed out by Maier and Haight,[17] the differential diagnosis between large, infected solitary cysts and empyema is at times extremely difficult, even impossible, to make preoperatively, and the true nature even at operation may not be recognized. If treated as an empyema, a striking feature in the postoperative course is the failure of the cavity to diminish progressively in size despite adequate dependent drainage.

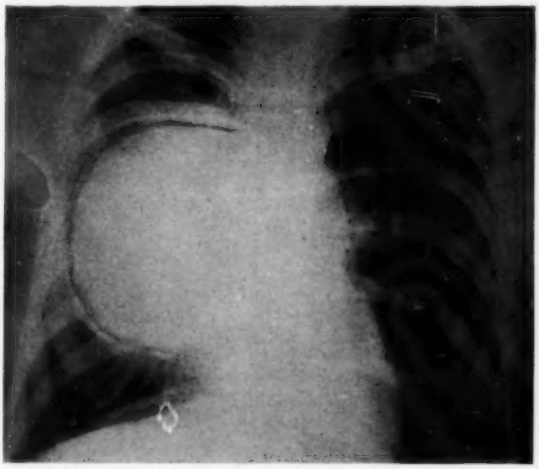


Fig. 4.—Posterior mediastinal tumor in a 9-year-old girl. The tumor was removed surgically; microscopic diagnosis was neurofibroma.

All individuals whose cystic disease produces symptoms should be subjected to surgery if they are physically fit. Extirpation of the cyst is the treatment of choice. In removal, normal lung should be spared where possible, and in most instances, enucleation of the cyst or lobectomy will be adequate. However, occasionally the cyst will represent almost the entire lung tissue and a pneumonectomy will be necessary (Fig. 5).

SUPPURATIVE LUNG DISEASE

Lung Abscess.—Abscess of the lung still presents a difficult problem to the thoracic surgeon. Whereas it has long been proved that medical treatment is ineffective and that it is best treated surgically, the ultimate results have not been completely satisfactory.[18]

Prompt and effective use of all measures available in prevention, and treatment in the acute phase, will reduce the number of chronic putrid lung abscesses. Medical management combines the proper use of antibiotics in parenteral, enteral, and aerosol administration; postural drainage, and frequent bronchoscopic aspirations for the detection and removal of any foreign bodies, and to more effectively promote drainage.

The mortality of chronic lung abscess ranges from 30 to 40 per cent.[18] In addition to this high mortality the disease carries a high morbidity. The clinical course is characterized by remissions and exacerbations, but even during the remissions the patient is plagued by cough, production of foul sputum, and hemoptysis.

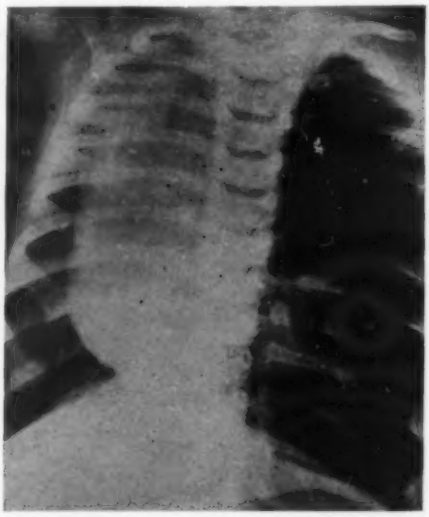


Fig. 5.—Large infected cyst in a 5-month-old baby. A pneumonectomy was necessary in this case, and a satisfactory result was obtained.

Glover and Clagett[19] have reported 37 cases of chronic lung abscess treated by pulmonary resection. Among 21 lobectomies there was 1 death, a bilobectomy patient. The remaining 20 patients were cured. However, of 16 pneumonectomies, 6 patients died postoperatively, and 3 additional ones died within five months, of a metastic brain abscess. An additional 3 patients had a serious complication. These results argue strongly for a surgical attack upon the lesion when lobectomy will suffice. Too often, even when seen early, medical management produces a remission and lulls the physician into a false sense of security.

The indications for primary resection in chronic lung abscess are: cases with secondary, presumably irreversible, changes; anatomically unsuited for drainage; excessive bleeding; patients with unremovable foreign bodies, complicated by bronchiectasis; perforation and localized empyema; atelectasis and pneumonitis unrelieved by bronchoscopic treatment.[18, 19, 20, 21] The treatment of choice would appear to be medical management in the acute phase with expectant observation, and early extirpation at the first sign of an unfavorable response, taking advantage of the medical routine as a preoperative preparation.

BRONCHIECTASIS

One of the common causes of cough is due to bronchiectasis. Laennec stated that out of every four cases in the adult, three had their origin in childhood. It is estimated that in children, bronchiectasis represents about 5 per cent of

all diseases.[22] The symptoms of bronchiectasis are many, with the triad of cough, sputum, and hemoptysis known to all. In addition to the distressing cough and production of foul sputum, the patients are subject to numerous upper-respiratory infections and recurrent attacks of pneumonitis. The disease is chronic, progressive, and downhill unless adequately treated.

Mallory[23] summarizes the present theories of pathogenesis as being: direct bronchial infection, congenital malformation of the bronchial tree, bronchial stenosis, pulmonary atelectasis, and pneumonitis. He concludes that the usual case is due to primary bronchitis and secondary atelectasis. Therefore, the best line of attack appears to be prevention or prompt alleviation of atelectasis.

In examining the morbidity and mortality rates of bronchiectasis it is apparent that some type of treatment is definitely needed. Perry and King,[24] on the basis of follow-up examination of 400 patients, concluded that in twelve years the mortality in the nonsurgically treated cases was 26 per cent; 41 per cent of the patients dying within five years of onset, and 15 per cent dying twenty years or longer after onset. In the fatal cases, 78 per cent died directly of the disease. There is evidence that patients developing bronchiectasis before the age of 10 do not live beyond the age of forty.[25]

The principal complications are empyema, direct extension of the infection, metastatic abscess (especially brain abscess), and hemoptysis. These definitely contribute to the mortality rate of bronchiectasis.

It is generally agreed that the definitive treatment of bronchiectasis is surgical. Although medical management may appear to alleviate the symptoms, it is only palliative, and the mortality and morbidity rates remain elevated. The treatment of choice is pulmonary resection early, when only a minimum of lung tissue must be sacrificed. Riggins[26] states that the physician who routinely advises young adults with operable bronchiectasis against surgery is assuming a great responsibility and in all probability renders his patient a great disservice.

The operative mortality in 122 lobectomies on 116 patients, reported by Churchill,[27] was 3 per cent. The working and living capacity was excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group. Kay and Meade[28] report a 1 per cent mortality for pulmonary resection in 100 patients. Bilateral lobectomy gives very gratifying results, although it is associated with a higher mortality. Churchill[27] reports 6 cases with 1 death. Strieder[25] reports 7 cases with 2 deaths.

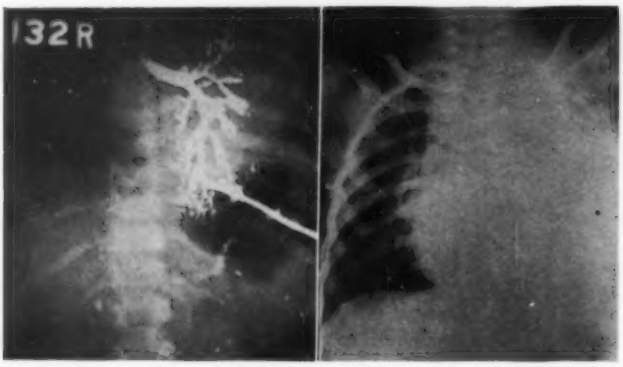
The author[29] reported 25 children with bronchiectasis treated by pulmonary resection. There was no mortality, although many were rather advanced cases with bilateral disease. The results were very gratifying; 64 per cent were considered cured; 28 per cent received a good result, meaning relief of all symptoms; and 8 per cent were improved.

The majority of patients with bronchiectasis should be considered for surgery. In children, especially, surgery should be advised since they stand lobectomy very well, and removal of the suppurative lung tissue will obviate the hazards of bronchiectasis which they must face if they grow to adult life without surgical treatment (Fig. 6).

CONGENITAL CARDIOVASCULAR DEFECTS

No discussion of thoracic surgery in pediatrics would be complete without some mention of the outstanding developments during the present decade in the surgical repair of certain congenital defects of the heart and great vessels.

There are the more common and better-known deformities, but in addition there are many rare types which have little more than academic interest. The present period of development was introduced with the first successful ligation of a patent ductus arteriosus by Gross[30] in 1938. This was followed by the report from Crafoord[31] of a successful operation for coaretation of the aorta in 1944; and Blalock,[32] who devised the procedure for congenital pulmonary stenosis and first performed the operation in 1944.



A. *B.*

Fig. 6.—*A*, Demonstration of bronchiectasis with involvement of the entire left lung, chronic empyema, and bronchopleurocutaneous fistula in a 3-year-old child. *B*, Postoperative pneumonectomy x-ray examination.

At least a working knowledge of the surgical approach to congenital anomalies of the cardiovascular system is necessary for the present-day clinician. However, as mentioned by Essrig,[33] whether such procedures should be carried out by the average well-trained surgeon in the average hospital is doubtful. Such detailed and complicated procedures demand the combined efforts of a skilled group of workers—cardiologists, pediatricians, surgeons, anesthetists, roentgenologists, and physiologists—if the desired results are to be obtained.

SUMMARY

1. A review of the more common thoracic surgical diseases in children has been presented. Illustrations of typical cases encountered are given.

2. Thoracic surgical procedures today are safe, and children suffering diseases amenable to surgery should be offered the chance of cure. Especially should surgery be offered to the young, as they tolerate surgery quite well, removal of suppurative disease decreases their morbidity and mortality rate, and the earlier the operation is performed the more the likelihood of a cure.

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Psychologic Aspects of Pediatrics

THE DEAF CHILD

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BY DEAFNESS is meant impairment of hearing to the extent that it is of no practical value for purposes of communicating with others. Included under this term, therefore, are not only the totally deaf but also individuals with some sound perception. Persons whose hearing is defective but functional, with or without a hearing aid, are considered the "hard of hearing" or the "partially deaf." The concept of deafness is being modified and many children whose hearing was formerly considered nonfunctional are now being helped by better hearing aids and improved training methods.

Schools for the deaf accept children with impaired hearing as well as those totally deaf. Many reports on the deaf also include the hard of hearing. The division between these two is useful but artificial as there is a gradual gradation in ability to hear.

INCIDENCE

The number of deaf and partially deaf in the United States has been variously estimated from one-half to one per 1,000 population. According to the White House Conference Report,[1] there were 2,000,000 school children with impaired hearing in 1930. This figure is generally considered too high. Of these, there were 17,000 whose hearing defect was severe enough to require instruction in lip reading.

ETIOLOGY

In 1927, a survey of 3,734 children in nineteen institutions and schools for the deaf was made.[2] There were 3,120 individuals in the Chicago area and a smaller group of 614 in the Philadelphia area. The results in the two groups corresponded closely. (Table I.)

It is very doubtful that there is total deafness in so many cases. Various other causes of deafness were reported including pneumonia, fever of unknown origin, whooping cough, and infantile paralysis each accounting for about 3 per cent of cases. Otitis media was associated with acquired deafness in only 20 per cent of the cases. Removal of tonsils and adenoids had no relation to lesions of the middle ear, total deafness, or partial deafness.

The majority of children with acquired deafness developed the defect before 3 years of age. (Table II.)

The more recent surveys[3, 4] have been made on smaller groups. The proportion of children found to be congenitally deaf has decreased to about 33 per cent. Deafness due to injury accounted for about 10 per cent of the cases. Respiratory

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diseases and otitis media led to deafness in only about 5 per cent of all cases. With the therapeutic agents at present available, deafness due to infectious disease may be expected to decrease.

Congenital deafness may be hereditary or it may be due to prenatal injury, the best known of which is German measles in the mother. Hopkins[5] was able to assemble 92 deaf children whose mothers had had rubella during the first three months of pregnancy.

Congenital deafness usually affects several members of the same family. In a survey made in 1911[6] it was found that 68 families contributed 161 children to one school for the deaf in less than a generation. The frequency of intermarriage among deaf persons tends to perpetuate the trait.

In the Chicago survey mentioned above[2] there was deafness in the families of the parents of 349 out of 3,120 deaf children; 345 deaf children had one or more siblings who were also deaf, 10 pairs were twins, and 3 deaf children each had 5 siblings who were deaf. In 23 instances the parents were first cousins, in 21 second cousins, and in 11 others they were related in some way. Fifteen of these children had a deaf mother, 8 a deaf father, and in 86 both parents were deaf.

The hearing of 454 children in the Pennsylvania School for the Deaf was examined in 1939 for both air and bone conduction.[7] Total loss of hearing was infrequent, only 5 per cent of the children being without some sensation from the auditory stimulus given by the audiometer. The conclusion was drawn that, if the group studied was representative, the number of those who can be helped to use their residual hearing is considerably greater than was formerly believed to be the case.

TABLE I. CHICAGO GROUP: 3,120 DEAF CHILDREN

CAUSES OF IMPAIRED HEARING	NUMBER	PER CENT
Congenital	*1,928*	*61.8*
Definite	1,419	
Probable	508	
No record	1	
Acquired	*1,192*	*38.2*
Meningitis	209	6.7
Total deafness	152	
Scarlet Fever	100	3.2
Total deafness	18	
Measles	97	3.1
Total deafness	8	
Influenza	91	2.9
Otitis media and mastoiditis	66	2.1
Accident	36	1.5
Skull Fracture	24	
Fall	12	
Unknown Etiology	286	9.2

TABLE II

AGE AT WHICH DEAFNESS WAS ACQUIRED	NUMBER	PER CENT
Under 3 years	706	59.23
3 to 10 years	337	28.26
Over 10 years	14	1.17
Unknown	135	11.19

In contrast with the deaf, the hard of hearing are able to develop language through normal channels though more slowly and with greater difficulty than normal children.[8] Their hearing is of use in everyday life. Estimates of the number of hard of hearing in the United States vary widely owing principally to (a) inaccuracies in measuring hearing loss and (b) a clear-cut definition of the extent of hearing impairment understood as "hard of hearing."

The hard of hearing have usually acquired speech before their hearing has become impaired and consequently they have a great advantage over the deaf. In their education, stress is placed upon the use of mechanical aids to increase hearing, lip reading to assist communication, speech correction, and voice training.

MENTAL FUNCTIONING

Impaired hearing in a child may produce behavior that is suggestive of feeble-mindedness. Hearing is important in the development of language on which depends, in turn, a considerable amount of general behavior. Special tests have been devised for the deaf which take into account their specific handicap in language development. In some of these tests pointing and gestures replace speech entirely in the directions. Most suitable for examining deaf children are performance tests such as form board tests, picture completion tests, block designs, and similar devices. For the older child directions may be written out and he then writes the answers. As deaf children often reply when only part of the direction is understood, it is most important for the tester to make sure that the entire question is comprehended.

The deaf child's lack of experience with such generally familiar objects as stamps, money, streetcars, etc., makes many tests used for normal children invalid even though verbal language is not involved. The Binet-Simon scale, in any of its modifications, even when substitutions eliminating language have been made, is therefore unreliable in the deaf. Almost all deaf children so tested have been found to score very low, the average mental retardation of 14 children tested in 1915 with a modification of the scale[9] being 3.4 years.

The Pintner-Paterson Performance scale was constructed with the deaf in mind. Pintner's Nonlanguage Mental test also has been used in many large surveys. Both are generally considered reliable for testing the deaf. Some use has been made of the Goodenough "Draw-a-Man" test. This seems to be valuable but the results are not as consistent as with the other tests.

Intelligence of the Deaf.—Most studies show the average intelligence of deaf children to be somewhat below that of hearing children. According to the best estimates at present available, the average intelligence quotient (I. Q.) of the deaf is a little below 90.[10] Two large surveys were carried out in the 1920's, the Reamer Survey[11] on 2,172 pupils and the National Research Council Survey[12] on 4,432 pupils in schools for the deaf. The average I. Q.'s in the former report for the middle age groups 12 to 15 years of age were 85 to 92, in the latter 82 to 86. In 1938 a comparison of the intelligence of deaf and hearing children[13] in New York City showed the results given in Table III.

The great difficulty in language may cause the deaf to score lower than their actual ability. There appear to be more slow and defective children among the

TABLE III

LEVEL OF INTELLIGENCE	DEAF (PER CENT)	HEARING (PER CENT)
Near genius	2	5
Very superior	13	15
Superior	13	15
Average	32	35
Dull	13	13
Borderline	15	11
Feeble-minded	12	7

deaf than among the hearing. The reason for this is not clear. That certain diseases, namely, those which affect the central nervous system, may lead to deafness and also impair mentality, does not seem to account for this entirely.

On the usual mental tests, the hard of hearing score slightly below hearing children.[14] This is probably due to impairment of language development as on nonlanguage tests they obtain scores similar to normal children. Educational achievement tests show the hard of hearing to be somewhat retarded. They are frequently grade repeaters in school. The greater the hearing loss the greater is the difficulty in keeping up with the normal child.

In the group of students at Gallaudet College for the Deaf, given the same test as students in colleges for the hearing, the median for the deaf fell below that for the hearing.[15] Nevertheless certain of the Gallaudet College students surpassed students from other colleges. Some deaf individuals have superior intelligence and can expect academic success in college even in competition with the hearing. Loring[16] believes that if a student who is hard of hearing is in the upper third of his class, he should be able to succeed in college without requiring special privileges, except front row seats for greater ease in lip reading. It may also be necessary to borrow lecture notes for review, as one cannot lip read and take notes at the same time.

The age at which the child becomes deaf has no effect upon the intelligence. No difference has been found between the average intelligence of the congenitally deaf and those with acquired deafness. Individuals totally deaf from birth have been able to compete in college as successfully as those who became deaf later on.

A slight difference in the achievement of deaf children taught by various methods has been observed. Those taught by the manual technique, i.e., gestures, finger-talking, and writing, scored somewhat lower than those taught by the oral method, i.e., lip reading and speech, or by the combined technique which included both methods. These results may be due to the fact that children who have difficulty in acquiring lip reading and speech are usually transferred to manual classes which therefore include the less bright children. Manual "thinking" is more concrete but less detailed and complete.

Language Functions.—In normal children language is acquired principally through hearing. When a child does not begin to speak at the expected age or when his speech is unintelligible or when simple words seem meaningless to him, a careful investigation of his hearing should be made. Because the deaf do not hear spoken language, they have great difficulty in learning to talk. The age at

which deafness begins has a definite effect. If the child is 4 years old or more at the time of becoming deaf he has a decided advantage, because language patterns have already been laid down.

When hearing is lost after normal speech has developed there is little difficulty in the production of speech sounds. The voice, nevertheless, is generally affected. The voice of the conduction-deaf individuals, in whom the middle ear is affected, is soft and low. His own voice which he hears by bone conduction, sounds louder than the voice of others; hence he lowers his voice. The perception-deaf person, on the other hand, in whom the inner ear is affected, speaks very loudly since he cannot hear his own voice. There is gradual loss of inflection and therefore need of constant practice to keep the tone.

Lesions of the middle ear may bring about an impairment in the conduction of sound, as a result of which, the threshold of auditory acuity is raised to a level where ordinary sounds do not penetrate with sufficient intensity.[17] On the other hand, lesions of the nerve fibers in the cochlea or along the auditory tract not only raise the threshold for sound but they distort it as well, resulting in an uneven impairment in hearing. Ordinary speech sounds range from approximately 250 to 4,000 cycles per second and the ready understanding of speech calls for a reasonable balance of hearing within this range. The person with nerve-type hearing impairment may hear the sounds in the lower part of this range reasonably well, yet he may not be able to hear the middle and upper parts well enough to distinguish many common speech sounds. The most important range for discrimination of vowel sounds is about 1,500 cycles per second while the ability to distinguish consonants lies between 2,000 and 4,000 cycles per second. With a serious impairment in the mid-high range, then, it is difficult to distinguish differences in consonants and such words as *bed, led, said, dead* sound very much alike to the afflicted person. It is apparent that such an impairment represents a serious interference with the acquisition of normal language habits.

Fairly good hearing for test-frequencies up to 1,000 cycles per second, but considerable or severe impairment for frequencies above this is common in cases of congenital, nerve-type hearing impairment.

The acquisition of language is slow and difficult for the deaf child and is probably the real reason for his poor educational achievement. The kinesthetic, tactual, and visual senses must be employed in speech education. The deaf child must be taught not how to hear a speech sound, but how to feel it and to imitate it and how to place and move his articulatory organs to produce speech. The percentage of residual hearing is very important in the acquisition of language.

Defective hearing and deafness can generally be detected by the usual hearing tests, such as the whispered voice, tuning fork, bell, clicker, and whistle. This technique does not identify the child with regional deafness, where hearing is lost for certain ranges of pitch only, nor does it distinguish degrees of hearing impairment. For these purposes the audiometer is most useful. It can be used for children 5 years of age and occasionally earlier. The difficulty lies in the fact that active participation is required of the child. Techniques are being investigated to eliminate this factor, using the principle of the conditioned reflex.

There is promise that a method will soon be perfected for measuring accurately auditory acuity of children after 10 months of age. Frequently there is potential residual hearing which is not being used but which can function with the help of a hearing aid or special training. The average deaf child never reaches the efficiency of a 9- or 10-year-old in the understanding and use of language, but with help, special training, and the realization that most so-called deaf children are not totally deaf, much more can be expected than hitherto.

There are a few objective tests for ability in lip reading and speech. These appear to correlate better with educational achievement than with intelligence.

Experience has shown that the deaf school child is inclined to make some kind of response whether or not he understands what is being said to him. When he understands only one or two words the answers may be irrelevant or peculiar. Even in written work he responds to any word that he knows and frequently fails because he did not understand the question. This "bluffing" leads to misunderstanding with friends and teachers and should be discouraged.

Reading is difficult for the deaf and in most instances remains so permanently. Experiments show that young deaf children can be taught to read much more efficiently than they do.[19] Reading can open fields of interest for the deaf which are hard for them to enter through conversation. It is therefore most important to encourage good reading habits and to provide adequate instruction. Books of high interest and low vocabulary level are needed.[20] Some deaf young people read with considerable ability and pleasure.

The deaf child is also inferior in written language. His sentences are simple in style, short, and somewhat rigid.[21] Lack of experience, limited scope of reading, and inability to hear adequately play a part here.

School.—Progress in school is painfully slow for the deaf child. By the time he is 12 to 14 years of age he is usually two or three years retarded in grade placement. The educational achievement of the deaf child is below what would be predicted from his intelligence.

In spite of their handicaps many deaf children achieve academic success. Timberlake and Montgomery[22] reported on 167 students who had graduated from colleges or universities for the hearing between the years 1928 and 1940. Some received graduate degrees. In certain fields such as science and mathematics, students from Gallaudet College for the Deaf exceeded the median for the colleges for the hearing.

Special Abilities.—The deaf do not seem to be handicapped in mechanical ability or in memory. It has been suggested that more emphasis be placed on mechanical, motor, and manual training in school. Shop work, home economics, trade training of all kinds, dramatics, gardening, and similar studies might well be emphasized in the training of the deaf child of normal or dull intelligence, and reading, writing and arithmetic, which are so difficult for him to grasp, should be subsidiary and incidental to these subjects.

PERSONALITY

There is a fairly definite personality pattern conceived of as belonging to the deaf. They are thought to be suspicious, selfish, treacherous, narrow, un-

sympathetic, and vindictive. Actually no personality pattern has been found consistently. They are said to be a little more unstable emotionally than the hearing, and they are somewhat more anxious.[23] Those who communicate by speech and lip reading are more like the hearing on inventory-questionnaires than those who rely on writing. As they grow older, other traits often become apparent such as possessiveness, a desire to attract attention, lack of foresight, little restraint, jealousy, irresponsibility, stubbornness, and rudeness. Simon[24] believes that these traits arise as a result of the exclusion of the deaf from responsibility and the consequent lack of development of a social sense.

According to Pintner deaf adults are more neurotic, introverted, and less dominant than the hearing.[25] Deaf children from homes where there are no other deaf people are somewhat less well adjusted than those with deaf relatives.[26] Other investigators[27] have found that deaf children were more rigid and less adaptable than either the blind or normal children. All of these tests seem inadequate as a technique of finding out how the deaf individual feels in a social situation.

The conclusion to be drawn is that the deaf vary in personality much as do the hearing. The parental attitudes, the individual's acceptance of his handicap, and his willingness and opportunity to mingle with normal society all have more bearing on his personality development than does his defect.

Children who are hard of hearing have the same potentialities for personality development as normal children. According to ratings by teachers, Madden[28] found that the partially deaf group showed more shyness, less aggressiveness, and less leadership than normal children. There was no difference in attentiveness, obedience, and social attitudes. In other tests the handicapped children have been found to be slightly more submissive and introverted. When loss of hearing amounts to 15 decibels or more, difficulties appear in adjustment. Although there is little difference in the personalities of hard of hearing and normal children in test situations, some of the hard of hearing admit to having more difficulty in making an adjustment to school. A few appear to be quite equal to the hearing necessary for good social adjustment.

Pintner studied the individual's feelings at the time he became aware of hearing loss. The shock was greatest if loss of hearing occurred in adolescence or early maturity and much less in childhood. Despair, resentment, humiliation, and shame were the most common reactions. These feelings do not occur in those deaf since infancy.

An important factor in the emotional development of the deaf child is the likelihood of his being sent to live in a residential school. The effect of removal from the home during the first six or seven years of life may be profound. A certain amount of regimentation is necessarily present in all boarding schools and an unemotional, impersonal attitude usually exists. Removal from home usually makes the child feel rejected and this is intensified if there are other siblings at home.

SCHOOLING

The number of residential schools for the deaf throughout the country is large. In general, the less bright children are sent to these schools, while those of higher intelligence are more likely to remain at home and attend day school.

This selective factor accounts, in part, for the better achievement on educational tests of children in day schools. In addition the latter usually begin their schooling earlier.

It requires three years of schooling for the deaf child to use and understand language well enough to do Grade I work.[29] This is an important reason for grade retardation. Training in language should therefore be started as early as possible. Even at 2 or 3 years of age the deaf child will benefit in nursery groups.

The academic standards in most schools for the deaf are below those of regular public schools in the same area. At the Illinois School for the Deaf the average achievement was only four-fifths of that of hearing children in the same grades. The older children were five years below average for their grade.

In 1944 there were 64 residential schools and 118 public day schools for the deaf throughout the United States. Methods of instruction vary. In most private schools and city day schools speech is used exclusively as the means of communication. In other schools, principally residential ones, speech is taught but it is not stressed and finger-counting and hand signs are permitted. Proponents of the latter type of school believe that, because the speech of the deaf usually remains peculiar, its acquisition is not worth the sacrifice of time and effort. This is not the opinion of most of the more experienced teachers who believe that even a little speech is an aid in socialization.[30]

Recent improvement in hearing aids has helped those who have some residual hearing and has assisted in finding some residual hearing in many individuals previously considered totally deaf. Less than two out of ten children in schools for the deaf have complete loss of hearing; not more than four out of ten have deficiencies greater than 75 per cent.[31]

OCCUPATIONS

Although much effort has been expended on vocational training for the deaf, its value is questionable. Martens[32] surveyed over 10,000 deaf and hard-of-hearing individuals who had received occupational training in school. Of these 37.4 per cent made no use of this training in later life and the others did to varying degrees. This survey revealed that success in the job was not related to the amount of previous vocational training. In another survey over one-half the deaf employed in one factory did exceptionally good work and only 2.5 per cent failed at their tasks. The most creditable work was done by those who had more than eighth grade education.[33]

It is hard for the deaf to get employment and hard for them to keep it. Their chief occupations are in unskilled and semiskilled work, such as laborers, porters, and domestics, but some hold positions in clerical occupations, as foremen and in semiprofessional services. Even when the job is done well there seems to be little chance of promotion. A larger percentage of the totally deaf who used only signs and gestures were employed than of those using spoken or written language. This is not what one would expect but may be due to the latter group desiring better positions and thus having to compete with normal individuals. There appears to be no field in which the deaf are particularly

competent, but the more intelligent have succeeded in such fields as printing, filing, and laboratory work. A few have become successful painters, cartoonists, and dress and jewelry designers.

During the recent war when opportunities for work were many, the deaf and hard of hearing were widely employed.

Deaf people are capable of driving automobiles successfully. In Pennsylvania[34] of 3,000,000 persons holding operators' licenses about 3,000 are "deaf mutes." Not one of these has ever been involved in a fatal accident. A rigid automobile test is required and this appears sufficient to insure successful driving by the deaf.

CARE OF THE DEAF CHILD

Deafness is not usually recognized in infancy. The handicap is diagnosed only when the delay in speech development is recognized, although the parent may have suspected it for some months. The shock of learning that the child is deaf is therefore not as great as in the case of the blind child.

Gesell[35] has listed signs suggestive of deafness in infants and young children in the developmental order in which they are most likely to appear.

I. *Hearing and Comprehension of Speech.*—
General indifference to sound,
Lack of response to spoken word,
Response to noises as opposed to voice.

II. *Vocalizations and Sound Production.*—
Monotonal quality,
Indistinctness,
Lessened laughter,
Meager experimental sound play and squealing,
Vocal play for vibratory sensation,
Head banging, foot stamping for vibratory sensation,
Yelling, screeching to express pleasure, annoyance, or need.

III. *Visual Attention and Reciprocal Comprehension.*—
Augmented visual vigilance and attentiveness,
Alertness to gestures and movement,
Marked imitativeness in play,
Vehemence of gestures.

IV. *Social Rapport and Adaptations.*—
Subnormal rapport in vocal nursery games,
Intensified preoccupation with things rather than persons,
Inquiring, sometimes confused or thwarted facial expression,
Puzzled and unhappy episodes in social situations,
Suspicious alertness, alternating with cooperation,
Markedly reactive to praise and affection.

V. *Emotional Behavior.*—
Tantrums to call attention to self or need,
Tensions, tantrums, resistances due to lack of comprehension,
Frequent obstinacies, teasing tendencies,
Irritability at not making self understood,
Explosions due to self-vexation,
Impulsive and avalance initiatives.

The evaluation of the degree of hearing present is complicated by the fact that a child may have an auditory impairment which interferes seriously with language development but he may be able to distinguish the sounds or feel the

vibrations of 256 or 512 double vibrations tuning forks and to respond to the low-frequency clicks and clapping of the hands that are commonly employed as the sole means to test hearing. Such a child, with some hearing but not enough, is usually slow to talk, his utterances are garbled and distorted, he often ignores commands and does not answer when spoken to, he is bored at home and inattentive at school, he does not play with other children, and he may present serious emotional disturbances such as shyness and reticence or noisy aggressiveness. Frequently he is regarded as mentally retarded. The observations of the parent may help in the clinical evaluation of the condition.

One of the primary needs of the deaf child is help in socialization, for it is because of isolation that many of the problems occur. From 6 months of age on, when the hearing child is experimenting with vocalization and adapting to sound in its environment, the deaf child becomes gradually more quiet, less responsive to speech, and at the same time more visually attentive. He is trying to make contact with the world socially through sight because he cannot comprehend through sound.

This is the time when the parent needs to use all possible means of communicating with the child and of helping him to understand. Pointing, gestures, dramatization all have their place in the environment of the deaf child. These aid him in understanding what is going on, and play an enormous part in his socialization. Socialization is necessary for optimum personality development.

If socialization is started early enough the child's natural desire to understand, to conform, and to receive approbation for behavior will be strengthened. When he can grasp something of what the parents are trying to show him, he will be more able to understand others who come into contact with him and will more easily fall into a social group.

In general, parents of handicapped children either feel resentful at their child's misfortune or they have a sense of guilt or embarrassment, believing that others will consider them in some way blameworthy. When possible they should be reassured that the condition is no fault of theirs or of their families. This may need to be reiterated frequently before it is accepted. The potentialities of the child should be stressed. The example of others, similarly afflicted, who have lived worth-while lives may help the parents to accept the disability. Agencies such as the Volta Bureau in Washington, the John Tracy Clinic in Los Angeles, and the League for Hard of Hearing in New York, can assist greatly in educating the parents. During the early years, the deaf child adjusts well in his home and learns with considerable facility except where language is concerned. Here the parent feels helpless and must seek aid.

The normal child learns to speak through imitation.[36] He sees the lips moving, hears a sound and imitates both lip movement and sound. The deaf child not only cannot hear or understand what is being said, he does not even know that there is speech nor that objects have names.

The deaf baby gurgles and coos in normal fashion and obviously is not mute. In fact "deaf and dumb" children are rare. Until recently many deaf people were not taught lip reading and speech properly and so were mistakenly thought to be mute. It is important from the very beginning to expose the deaf child to a constant flow of language. As most infants are not completely deaf

some sound will get through. In this way the child becomes conscious of speech. The small remnant of hearing present should be developed and utilized to the fullest. The fact that the child cannot understand is no reason for not talking to him. The normal infant of 6 months cannot understand either; parents nevertheless talk to their babies. Nor do they use only one-syllable words with their one-year-olds. Instead they converse much as with older people but a little more consciously, naming objects and pointing out activities. This is just what the parent of the deaf child should do. Talk, talk, talk, is the advice given by all the agencies to parents of deaf children. The deaf baby should be given at least the same exposure to language as the hearing child.

The mother should talk close to the baby's ear. Inasmuch as the hearing range may be only a few inches the child may be unable to hear at all at the usual distance. She should show him objects and name them, being sure that the baby sees at the same time both the object and the movement of her lips. After he is a year old she can place his fingers on her lips as she speaks. Many deaf children learn considerable lip reading before 2 years of age.

The more people who talk to the child the better his lip reading will be. There are a few suggestions which will make learning easier.[37] The light should be on the face of the person speaking so that the child can more easily see him. The head should be kept as still as possible so as not to distract the child from the difficult task of watching lip and tongue movement. When possible the speaker's face should be on a level with the child's face. Whole sentences and good language are important, exaggeration of movement and mouthing of words make understanding more difficult. It is well to speak a little more slowly but pauses should come only in the natural places. If the child can be told something in the present or something concrete there is more probability that he will understand. "It's time to get dressed" or "let's turn on the radio" will have more meaning for the child than a discussion of the previous day's activities. Some children are more adept at learning lip reading than others but eventually, with patience on the part of the parent, the child will learn.

Other sounds should be brought into the child's environment such as musical blocks, squeak toys, and bells; and the child's attention should be called to the general sounds of daily life, fire whistles, automobile horns, church bells, and other common sounds.

There are other ways in which the parent can help the deaf child to learn. Imitation is the beginning of education. Matching one thing to another is imitation. The deaf child should be taught to match colors, objects, sizes, shapes. Later he can match a picture to an object, a picture to a picture, a written name to a picture, and finally a picture to the movement of the lips as the word is spoken. Thus he will learn to lip-read and to understand, and when he learns to speak it will be meaningful. When he is able to understand he will no longer be shut off from the world about him.

The actual teaching of speech is best left to someone who has had training. There are private nursery schools for deaf children under 3 years of age. Certain residential schools admit children at 3 years and many others have nursery departments for slightly older children. Some day schools for the deaf now

have preschool classes. Many of these are open to mothers also for instruction. The deaf child should have an opportunity to learn speech as early as possible.

Fortunately there are many boarding and day schools for school-age deaf children. In some cities there are accredited high schools for the deaf; elsewhere, the children are graduated from elementary schools with normally hearing children. In Illinois the children who can benefit by the use of hearing aids are given special training in the State School for the Deaf and then returned to public school at as early an age as possible. The only college exclusively for the deaf is Gallaudet College in Washington, D. C. which includes three years of high school and two of college. The oral method is now being introduced.

The associated difficulty in speaking and reading is really a greater handicap than the deafness.[38] It is therefore of first importance that the child acquire a good command of language.

Hearing Aids.—Various types of hearing aids are available for bone and air conduction. They should be carefully selected.[39] They are especially valuable for improving natural articulation and rhythm in speech of young, deaf children who are just learning to talk.[40] Proper instruction in the use of the instruments for various sounds, instrumental and vocal music, the spoken voice, telephone voices, with and without background noises, should be given. Deaf and partially deaf children should become accustomed to wearing these aids as early as possible, since a period of adjustment is necessary before amplified sound can be understood. Most persons hear best with a device that amplifies all sound frequencies uniformly regardless of individual defects and audiogram variations.

Hearing aids have been greatly improved since World War II. The newer instruments have smaller, more compact and more efficient batteries than formerly. Extraneous noises, such as result from rubbing of clothing, have been reduced and the ear receivers are smaller. With a properly fitted instrument, a gain of 40 to 50 decibels is possible instead of the 30-decibel improvement considered excellent after the fenestration operation. There is some difference of opinion as to how young a child can use an individual hearing aid. Certain children have used them successfully at 2 or 3 years; most are able to do so by school age.

Table amplifiers similar to "loud speakers" can benefit young children and are often of assistance in getting older individuals to accept an aid. In some schools these amplifiers are used in class to increase the volume of the voice and thus assist in comprehension of directions and discussion. Lip reading should not be neglected. It enhances greatly the effectiveness of hearing aids.

Training.—Except where communication is necessary the deaf child is not at a great disadvantage. He can learn to walk and run, to feed himself, to undress and dress, and he can be toilet-trained at the usual times. He must be allowed to grow up and to become independent just as any normal child. The deaf child should be given many things to do. Because abstract ideas will be difficult for him to grasp, he should be started early with constructive play things. Paints, hammer and nails, mechanical toys, whatever he can do with his hands will help later on. A diversity of occupations will give him more interests in life also.

When he is old enough, rhythm, dancing, exercises, and sports should be started. Not only are rhythm and dancing important in relation to speech work, but these are new interests where he can be successful.

In teaching reading, the books used should be simple in language because the vocabulary of deaf children is very limited. If pressed too hard or if the books are too difficult he may lose interest. This would be unfortunate because reading opens the road to much that the deaf can never experience first hand. If the child has a normal intelligence and is taught correctly, he can learn to read.[41] For the bright deaf child, books are an absorbing pleasure.

At times disciplinary problems arise because of the child's inability to understand directions. Before undertaking disciplinary measures it is essential that the parent be sure that he has spoken clearly and that the child has really understood what has been said.

The deaf child is not as isolated as the blind child and hence not so egocentric. Every effort should be made to provide play outlets and companionship for him. In this way he gains confidence and learns to be comfortable in the society of many people. He should be permitted to use gestures and motions during group play as this provides him with a feeling of freedom which would be impossible for him with other means of expression. Too much emphasis on speech and lip reading may dampen his spirits and make him self-conscious. He should be included in family conversation and decision, otherwise he may acquire the habit of not listening or watching and consequently he will have more difficulty in learning to lip read, and because he cannot hear what is said, as he grows older he may interpret conversations as being disparaging to him. The child's self-esteem must be built up. As congenital deafness is often not discovered until late in the first year of life, the parents have had time to love and enjoy their baby and treat him as any other child. This is a great advantage for the deaf child over the blind child. The best advice to the parents is that they continue to treat him in just the same way, not spoiling him or feeling sorry for him.

The parent should understand that the personality defects which a deaf child may exhibit are not implicit in his handicap but develop because of limitations of social contacts and improper attitudes on the part of parents. What is frequently forgotten is the need of the child to have many and new experiences. Only in this way will he mature normally. The parent should be aware of this need and should help to provide the child with proper opportunities. He must be expected to take responsibility and given privileges for which he is ready. Success and being needed are even more important to the handicapped than to the normal child. Early independence, travelling, shopping, and going places alone will give him confidence.

Full acceptance of the child in the family is of great importance. The attitude taken by the parents and siblings will influence the attitude of others with whom he comes in contact. The child must know that he is loved and wanted, that there is a definite place for him in the family, and that he is not thought of as different from his brothers and sisters.

"The aim of education . . . should be . . . to produce happy, well-adjusted deaf individuals, each different from the other, each with his own personality and not pale imitations of hearing persons." (Pintner and associates.[18])

Information regarding all aspects of the care of the deaf can be obtained from:

American Hearing Society, 817 14th Street, Washington 5, D. C.
John Tracy Clinic, 924 West 37th Street, Los Angeles 7, California.
New York League for the Hard of Hearing, 480 Lexington Avenue, New York 21, N. Y.
The Volta Bureau, 1537 35th Street, Washington 7, D. C.

Pamphlets which may be recommended to parents are:

Montague, H.: John Tracy Clinic Correspondence Course, from the John Tracy Clinic.

Ronnei, E. C.: Help for the Hard of Hearing, National Parent-Teacher, Chicago, May, 1946.

Sutherland, D. T., and Miller, M.: Rehabilitating the Hard of Hearing Child, U. S. Department of Labor, Washington, D. C.

Tracy, L. T.: New Avenues to Understanding, from the John Tracy Clinic.

Tracy, L. T.: Suggestions to the Parents of Deaf and Hard of Hearing Children, from the John Tracy Clinic.

Wood, K. S.: Mental Hygiene for the Hard of Hearing, from the American Hearing Society.

Book:

Heiner, M. H.: Hearing Is Believing, Cleveland and New York, 1949, World Publishing Company.

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News and Notes

Dr. John C. Gittings, of Philadelphia, died March 9, 1950, at the age of 75. After receiving his medical degree from the University of Pennsylvania in 1895, he became associated with the Children's and St. Christopher's Hospitals. He started teaching at the University of Pennsylvania Medical School in 1904, and in 1920 organized the department of pediatrics in the graduate school. In 1924 he became professor of pediatrics. In 1930 he moved to Maryland where he became a visiting lecturer in pediatrics at Johns Hopkins. In 1933 he returned to Philadelphia as the Bennett Professor of Pediatrics. For many years he was on the editorial board of the American Journal of Diseases of Children, and was co-author on two texts, one on infant feeding and one on tuberculosis in childhood. He was a member of the Pediatric Society and served as president in 1928.

Two Research Fellowships in pediatric allergy are offered by the Pediatric and Immunology Departments of the New York Medical College, 106th Street and Fifth Avenue, New York, N. Y.

These fellowships will be full time. One starts July 1, the other, January 1. Stipend to be arranged. Applicants must be certified in pediatrics or have the requirements for certification. The fellowships run from one to two years and will consist of intensive training in immunology and animal research pertaining to the field of hypersensitiveness; intensive study of allergic children will include skin testing, laboratory work, clinical follow-up, as well as clinical research. Applicants who have had previous training in chemistry and/or immunology, and who are desirous of a research career will have preference.

Applications should be made to the Office of the Dean.

The **Bureau of Vital Statistics** on March 27 released figures on the Infant Mortality Rate for 1948. There were 3,535,068 living births in 1948 with 113,169 deaths under one year of age, making a rate of 32. This is the lowest rate ever recorded and is 0.2 of a point under the rate for 1947. The state with lowest rate was Connecticut with 24.3 and the highest was 70.1 for New Mexico. There were very slight differences by states from the 1947 rates, but all states showed a lower rate than in 1946 when the rate for the country as a whole was 47. One-third of the deaths occur in the first week of life with the peak in the first day of life. A second third takes place in the first month, and the final third is spread over the remaining eleven months. The IMR has been reduced by 50 per cent since 1930 when it stood at 64.6 per 1,000 live births. The greatest reduction has been in the 6- to 11-month age period which has fallen 72 per cent since 1930 or from 10.7 to 3.0 in 1948. Premature birth continues to be the leading cause of death and accounts for 11.1 deaths in the 32.

The Virginia Pediatric Society will hold its annual Spring Scientific Meeting on Friday and Saturday, May 5 and 6, 1950, at Hotel Roanoke, Roanoke, Va.

The University of Arkansas announces the acceptance of a gift of 500,000 dollars from the William Buchanan Foundation of Texarkana, Ark. This gift will be used exclusively for the Department of Pediatrics of the School of Medicine principally to construct an additional 100 pediatric beds in the new University Hospital. This will be known as the William Buchanan Pavilion for Children. Construction will probably start before the end of 1950. Negotiations with the Foundation were carried out by Dr. Wm. A. Reilly and the University authorities.

Book Reviews

Het rubella-probleem in het licht van Nederlandse ervaringen (The Rubella Problem in the Light of Dutch Experiences). Dr. A. Elisabeth H. M. Kamerbeek, with cooperation of Henriëtte A. van Gilse, H. W. Hildernisse, and C. A. G. Nass, H. E. Stenfert Kroese's Uitgevers-Mij. N. V., Leiden, The Netherlands.

When after the war the discovery of Gregg of the relation between congenital malformations and rubella infection during the early months of pregnancy became known in the Netherlands, a committee was appointed to study this important problem and if possible to indicate preventive measures. Professor van Gilse was appointed president of this committee at Leiden, and Dr. Kamerbeek, secretary. Dr. Kamerbeek has collected the Dutch experiences in her thesis, which appeared at the same time as a treatise from the institute for preventive medicine at Leiden.

By means of inquiries, 105 cases of congenital defects after rubella, or a rubella-like disease, during pregnancy of the mother were collected. The conception of Carruthers about the nature and extension of the malformations in relation to the moment of infection was completely confirmed.

An extensive discussion is given of the clinical picture of rubella including the differential white blood cell count, of the prophylactic possibilities, and of the literature on the subject. The preventive effect of rubella convalescent serum was studied but could not be proved definitely.

S. v. C.

Mental Hygiene in Public Health. Paul V. Lemkau, M.D., New York, 1949, McGraw-Hill Book Company, Inc., 396 pages. Price $4.50.

This text presents in large part the course in mental hygiene given to the students in the School of Hygiene and Public Health of the Johns Hopkins University, in which the author is Associate Professor of Public Health Administration and Director of the Mental Health Study of the school. Although care of the mentally ill forms perhaps the largest morbidity problem in medicine, it is only beginning to be looked upon as a problem of public health, and up until a year or so ago at least, it was considered from this viewpoint by only one of the schools of public health. Thus Dr. Lemkau's text is distinctly a pioneer effort. Any solution of the problem of the mentally ill and maladjusted individual must eventually depend on prevention, and hence it is this aspect that is stressed. The paucity of our knowledge of prevention is clearly demonstrated by the text and it will be interesting in the future to compare this volume with texts written, say, ten to twenty years ago. The pediatrician will find much of interest, as he has been aware that the treatment of the maladjusted and problem child is one of prevention, and a number of pediatricians, like Aldrich and Spock, have made distinct contributions. Much of the text is given to the discussion of the development of the individual at various age periods (from the prenatal through the adolescent) which come within his field. The reviewer feels that the text has a much broader field than one limited to the students in a school of public health, and should have a wider audience.

Allergy in Relation to Otolaryngology. French K. Hansel, M.D., St. Paul, 1949, The Bruce Publishing Company, 77 pages. Price $2.50.

This is a panel discussion issued as an official publication of the American College of Allergists. Dr. Hansel was the chief speaker. He has presented in detail the cytologic picture of nasal and sinus secretions seen in allergy and in infants. Other allergists, including Goldman and Kafke of New York and Jerome Glaser of Rochester, have continued the panel with discussions of special phases.

Editor's Column

THE ANCIENT RITE OF CIRCUMCISION

WHETHER or not circumcision is a useful procedure is widely debated by physicians but the pediatric literature is strangely silent on this subject. Originally practiced as a religious rite or a tribal custom, circumcision has in more recent years received the stamp of approval of medical authority. A critical survey by Gairdner in a recent issue of the *British Medical Journal*, as well as a discussion of the hygiene of the prepuce, is therefore, most welcome.

The practice of circumcision is an ancient one. It was already widespread some 15,000 years ago at the very dawn of history. The earliest Egyptian mummies, dating back to 2300 B.C., were circumcised. Columbus found that many American Indians had had the operation. At present, and for as long as we can tell, circumcision has been performed by about one-sixth of the world population—in the Near East, in some parts of Africa, among the Moslem peoples of India and Southeast Asia, and among the Australasian aborigines. Among Western nations the operation is at present widely practiced only by the English speaking peoples and by adherents of the Jewish faith.

In England the frequency with which the operation is performed varies considerably in different sections of the country and in different social strata. In Newcastle upon Tyne 12 per cent of males were found to be circumcised by one year of age. In Cambridge there were 31 per cent. Among boys coming from the upper classes in the Cambridge area the percentage at 13 years was 67, while among boys from the general schools only 30 per cent had been operated upon.

Gairdner discusses, at some length, phimosis which is the most frequent reason given for nonritual circumcision. The prepuce in the newborn infant is nearly always nonretractable and remains so for much of the first year of life and often longer. Anatomic studies show wide variations in the degree of separation of prepuce and glans. It is uncommon for the two to be completely separated at birth. In most instances the division is only partial and in some full-term males it has not yet begun.

If left alone only about 10 per cent of boys fail to show a retractible prepuce by 3 years of age, and in most of these retractibility can be effected by gentle manipulation. Gairdner therefore urges against the common practice of separating and stretching the foreskin in young children. Despite the small size of the preputial orifice it is, with rare exceptions, adequate for micturition. Drawing back the prepuce not only is unphysiologic; it is unnecessarily painful and traumatizing as well. The relative infrequency of ulcerated meatus in the uncircumcised male is a measure of the protective function of the prepuce.

After about three years, drawing back a hitherto unretracted foreskin reveals inspissated smegma which is often malodorous. When the prepuce remains difficultly retractible after this age circumcision should be considered.

Of the various reasons given for circumcision aside from phimosis-balanitis, posthitis (inflammation of the glans), enuresis, and masturbation, Gairdner con-

siders none valid except penile cancer. All observers agree that circumcision, performed during the first five years of life, protects absolutely against this rare disease. The reason is not clear.

Aside from the inconvenience and expense of the operation and the anxiety which is associated with it, about sixteen deaths in children under 5 years of age occur each year in England as a result of circumcision. Hemorrhage, sufficient to require transfusion, is a not infrequent complication.

Gairdner concludes that the prepuce of the young infant should be left in its natural state. As soon as it becomes retractible, generally between 9 months and 3 years of age, its toilet should be included in the routine of the bath time and soap and water should be applied as to other parts of the body. As the boy grows up he should be taught to keep his prepuce clean just as he is taught to wash his ears.

Shaw, in a discussion of the "Most Unphysiological Period of Life" (by which he means the neonatal period), has also raised his voice against circumcision. He says, "The baby boy has further unhappiness imposed upon him when (almost invariably) he is circumcised. The physiological reasons for this practice escape me although it is a venerable religious rite. Mothers usually either demand it or simply accept it as the proper thing. What little can be said in its favor, perhaps with respect to cleanliness, apparently appeals to the mother who is, after all, a female, but this little is persuasively outweighed by the pain and risk thus inflicted and by the lack of any good physiological reason for it. I should be loath to imply that any serious psychic or somatic damage is thus usually inflicted although there are extant in medical writings a few bitter protests from elderly—and presumably circumcised—physicians against it."

It seems evident then that, except for the prevention of penile cancer, there is no good reason for the routine circumcision of boys; and there are objections. Moreover, the painful and traumatic manipulations of the prepuce, being unnecessary, should be eliminated.

H. B.

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VITAL STATISTICS, 1948

THE annual report of the Public Health Service for 1949 contains some interesting data on vital statistics for the year 1948. The death rate for 1948 was the lowest on record, 9.9 per 1,000 population. There were approximately 3,700,000 births which is slightly under the high peak of 1947. The Infant Mortality Rate reached a new low of 31.8, which reflects a cut of two-thirds in the last thirty years. The lowest death rate is the 5- to 14-year age group with a rate of 0.7 per thousand. The age group showing the greatest decrease since 1940 is the 1- to 4-year group which shows a decrease of 40 per cent from a rate of 2.9 in 1940 to 1.6 in 1948. With this lowering of the mortality rate in the early age periods, the average length of life for an individual increased to 67.2 in 1948 from 66.8 in 1947. Premature birth is still one of the ten leading causes of death.

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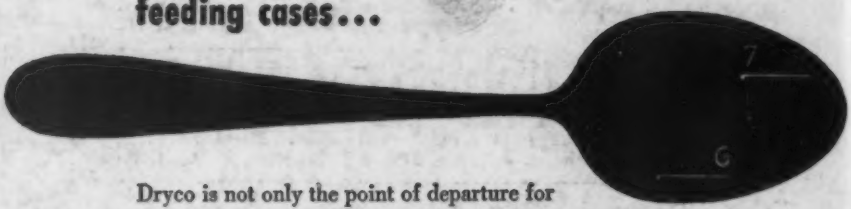

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